(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68867 A1

(51) International Patent Classification⁷: C12N 15/52, 15/76, C12P 17/18, 19/44, 19/62, C12Q 1/68, C07H 17/08, 19/01

(21) International Application Number: PCT/GB00/02072

(22) International Filing Date: 30 May 2000 (30.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9912563.5 28 May 1999 (28.05.1999) GB

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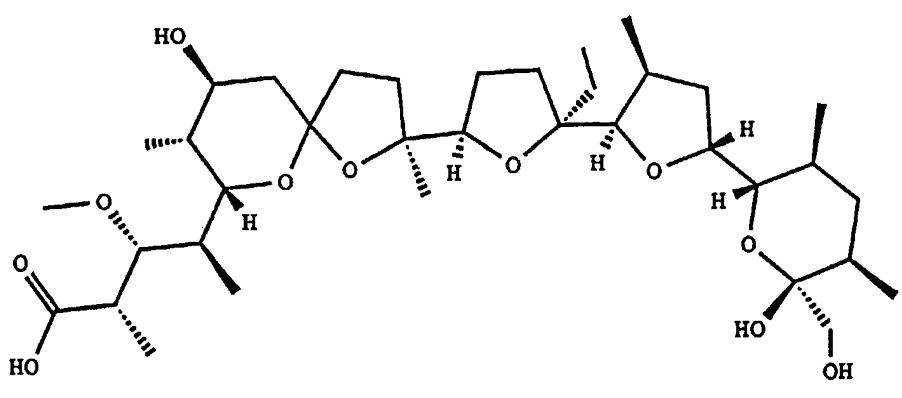
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: POLYKETIDES AND THEIR SYNTHESIS



monensin A : R = ethyl
monensin B : R = methyl

(57) Abstract: The complete sequence of the gene cluster for the monensin type I polyketide synthase, from *S. cinnamonensis*, is provided. Thus variant polyketides containing monensin-derived elements can be genetically engineered. Furthermore there are features, e.g. a regulatory protein *mon RI*, which are of wide utility.

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— *with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description*

POLYKETIDES AND THEIR SYNTHESIS

The present invention relates to processes and materials (including enzyme systems, nucleic acids, vectors and cultures) for preparing polyketides, particularly polyethers but including polyenes, macrolides and other polyketides by recombinant synthesis, and to the polyketides so produced, particularly novel polyketides. (N.B the term "polyketide" is being used in its conventional sense to include structures notionally derived by the reduction and/or other processing or modification of one or more Ketide units). Furthermore the invention provides the entire nucleic acid sequence of the biosynthetic gene cluster that governs the production of the ionophoric antibiotic polyether polyketide monensin in *Streptomyces cinnamonensis*, and the use of all or part of the cloned DNA first, in the specific detection of other polyether biosynthetic gene clusters; secondly in the engineering of mutant strains of *S. cinnamonensis* and of other actinomycetes which are suitable host strains for the high level production of novel recombinant polyketides; and thirdly in the provision of recombinant biosynthetic genes which lead to such novel polyketide products.

Polyketides are a large and structurally diverse

class of natural products that includes many compounds possessing antibiotic or other pharmacological properties, such as erythromycin, tetracyclines, rapamycin, avermectin, monensin, epothilones and FK506. In particular, polyketides are abundantly produced by *Streptomyces* and related actinomycete bacteria. They are synthesised by the repeated stepwise condensation of acylthioesters in a manner analogous to that of fatty acid biosynthesis. The greater structural diversity found among natural polyketides arises from the selection of (usually) acetate or propionate as "starter" or "extender" units; and from the differing degree of processing of the β-keto group observed after each condensation. Examples of processing steps include reduction to β-hydroxyacyl-, reduction followed by dehydration to 2-enoyl-, and complete reduction to the saturated acylthioester. The stereochemical outcome of these processing steps is also specified for each cycle of chain extension. In addition, the biosynthetic pathways to many polyketides involve additional enzyme-catalysed modifications which may include: methylation by O- and C-methyltransferases, hydroxylation by cytochrome P450 enzymes, other oxidation or reduction processes, and the biosynthesis and attachment of novel sugars and/or deoxy sugars.

The biosynthesis of polyketides is initiated by a group of chain-forming enzymes known as polyketide synthases. Two classes of polyketide synthase (PKS) have been described in actinomycetes. One class, named Type I PKSs, represented by the PKSs for the macrolides erythromycin, oleandomycin, avermectin and rapamycin, consists of a different set or "module" of enzymes for each cycle of polyketide chain extension. (For examples see Cortés, J. *et al.* Nature (1990) 348:176-178; Donadio, S. *et al.* Science (1991) 252:675-679; Swan, D.G. *et al.* Mol. Gen. Genet. (1994) 242:358-362; MacNeil, D.J. *et al.* Gene (1992) 115:119-125; Schwecke, T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843.)

The term "extension module" as used herein refers to the set of contiguous domains, from a β-ketoacyl-ACP synthase ("KS") domain to the next acyl carrier protein ("ACP") domain, which accomplishes one cycle of polyketide chain extension. The term "loading module" is used to refer to any group of contiguous domains which accomplishes the loading of the starter unit onto the PKS and thus renders it available to the KS domain of the first extension module. The length of polyketide formed has been altered, in the case of erythromycin biosynthesis, by specific relocation using genetic engineering of the enzymatic domain of the erythromycin-

producing PKS that contains the chain releasing thioesterase/cyclase activity (Cortés J. *et al.* Science (1995) 268:1487-1489; Kao, C.M. *et al.* J. Am. Chem. Soc. (1995) 117:9105-9106).

In-frame deletion of the DNA encoding part of the ketoreductase domain in module 5 of the erythromycin-producing PKS (also known as 6-deoxyerythronolide B synthase, DEBS) has been shown to lead to the formation of erythromycin analogues 5,6-dideoxy-3-α-mycarosyl-5-oxoerythronolide B, 5,6-dideoxy-5-oxoerythronolide B and 5,6-dideoxy,6-β-epoxy-5-oxoerythronolide B (Donadio, S. *et al.* Science (1991) 252:675-679). Likewise, alteration of active site residues in the enoylreductase domain of module 4 in DEBS, by genetic engineering of the corresponding PKS-encoding DNA and its introduction into *Saccharopolyspora erythraea*, led to the production of 6,7-anhydroerythromycin C (Donadio, S. *et al.* Proc. Natl. Acad. Sci. USA (1993) 90:7119-7123).

International Patent Application number WO 93/13663 describes additional types of genetic manipulation of the DEBS genes that are capable of producing altered polyketides. However many such attempts are reported to have been unproductive (Hutchinson, C.R. and Fujii, I. Annu. Rev. Microbiol. (1995) 49:201-238, at p. 231). The complete DNA sequence of the genes from *Streptomyces*

hygroscopicus that encode the modular Type I PKS governing the biosynthesis of the macrocyclic immunosuppressant polyketide rapamycin has been disclosed (Schwecke, T. *et al.* (1995) Proc. Natl. Acad. Sci. USA 92:7839-7843). The DNA sequence is deposited in the EMBL/Genbank Database under the accession number X86780.

WO 98/01546 discloses that a PKS gene assembly (particularly of Type I) encodes a loading module which is followed by at least one extension module. The first open reading frame encodes the first multi-enzyme or cassette (DEBS1) which consists of three modules: the loading module (ery-load) and two extension modules (modules 1 and 2). The loading module comprises an acyltransferase and an acyl carrier protein. This may be contrasted with Figure 1 of WO 93/13663 (referred to above). This shows ORF1 as only two modules, the first of which is in fact both the loading module and the first extension module.

WO 98/01546 describes in general terms the production of a hybrid PKS gene assembly comprising a loading module and at least one extension module. It also describes (see also Marsden, A.F.A. *et al.* Science (1998) 279:199-202) construction of a hybrid PKS gene assembly by grafting the wide-specificity loading module for the avermectin-producing polyketide synthase onto the first

multi-enzyme component (DEBS1) for the erythromycin PKS in place of the normal loading module. Certain novel polyketides can be prepared using the hybrid PKS gene assembly, as described for example in WO 98/01571.

WO 98/01546 further describes the construction of a hybrid PKS gene assembly by grafting the loading module for the rapamycin-producing polyketide synthase onto the first multi-enzyme component (DEBS1) for the erythromycin PKS in place of the normal loading module. The loading module of the rapamycin PKS differs from the loading modules of DEBS and the avermectin PKS in that it comprises a CoA ligase domain, an enoylreductase ("ER") domain and an ACP, so that suitable organic acids including the natural starter unit 3,4-dihydroxycyclohexane carboxylic acid may be activated *in situ* on the PKS loading domain and, with or without reduction by the ER domain, transferred to the ACP for intramolecular loading of the KS of extension module 1 (Schwecke, T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843). WO 98/51695 and WO 98/49315 describe additional types of genetic manipulation of the DEBS genes that are capable of producing altered polyketides.

The second class of PKS, named Type II PKSs, is represented by the synthases for aromatic compounds. Type II PKSs contain only a single set of enzymatic activities

for chain extension and these are re-used as appropriate in successive cycles (Bibb, M.J. *et al.* EMBO J. (1989) 8:2727-2736; Sherman, D.H. *et al.* EMBO J. (1989) 8:2717-2725; Fernandez-Moreno, M.A. *et al.* J. Biol. Chem. (1992) 267:19278-19290). The "extender" units for the Type II PKSs are usually acetate units, and the presence of specific cyclases dictates the preferred pathway for cyclisation of the completed chain into an aromatic product (Hutchinson, C.R. and Fujii, I. Ann. Rev. Microbiol. (1995) 49:201-238). Hybrid polyketides have been obtained by the introduction of cloned Type II PKS gene-containing DNA into another strain containing a different Type II PKS gene cluster, for example by introduction of DNA derived from the gene cluster for actinorhodin, a blue-pigmented polyketide from *Streptomyces coelicolor*, into an anthraquinone polyketide-producing strain of *Streptomyces galileus* (Bartel, P.L. *et al.* J. Bacteriol. (1990) 172:4816-4826).

The minimal number of domains required for polyketide chain extension on a Type II PKS when expressed in a *Streptomyces coelicolor* host cell (the "minimal PKS") has been defined for example in WO 95/08548 as containing the following three polypeptides which are products of the *actI* genes: firstly KS; secondly a polypeptide termed the CLF with end-to-end

amino acid sequence similarity to the KS but in which the essential active site residue of the KS, namely a cysteine residue, is substituted either by a glutamine residue or, in the case of the PKS for a spore pigment such as the *whiE* gene product (Davis, N.K. and Chater, K.F. Mol. Microbiol. (1990) 4:1679-1691) by a glutamic acid residue; and finally an ACP. The CLF has been stated (for example in WO 95/08548) to be a factor that determines the chain length of the polyketide chain that is produced by the minimal PKS. However it has been found (Shen, B. *et al.* J. Am. Chem. Soc. (1995) 117:6811-6821) that when the CLF for the octaketide actinorhodin is used to replace the CLF for the decaketide tetracenomycin in host cells of *Streptomyces glaucescens*, the polyketide product is not found to be altered from a decaketide to an octaketide, so the exact rôle of the CLF remains unclear. An alternative nomenclature has been proposed in which KS is designated KSα and CLF is designated KSβ, to reflect this lack of knowledge (Meurer, G. *et al.* Chemistry & Biology (1997) 4:433-443). The mechanism by which acetate starter units and acetate extender units are loaded onto the Type II PKS is not known, but it is speculated that the malonyl-CoA: ACP acyltransferase of the fatty acid synthase of the host cell can fulfil the same function for the Type II PKS (Revill, W.P. *et al.* J.

Bacteriol. (1995) 177:3946-3952).

WO 95/08548 describes the replacement of actinorhodin PKS genes by heterologous DNA from other Type II PKS gene clusters, to obtain hybrid polyketides. It also describes the construction of a strain of *Streptomyces coelicolor* which substantially lacks the native gene cluster for actinorhodin, and the use in that strain of a plasmid vector pRM5 derived from the low-copy number vector SCP2* isolated from *Streptomyces coelicolor* (Bibb, M.J. and Hopwood, D.A. J. Gen. Microbiol. (1981) 126:427-442) and in which heterologous PKS-encoding DNA may be expressed under the control of the divergent *actI/ actIII* promoter region of the actinorhodin gene cluster (Fernandez-Moreno, M.A. *et al.* J. Biol. Chem. (1992) 267:19278-19290). The plasmid pRM5 also contains DNA from the actinorhodin biosynthetic gene cluster encoding the gene for a specific activator protein, ActII-orf4. The ActII-orf4 protein is required for transcription of the genes placed under the control of the *actI/actIII* bidirectional promoter and activates gene expression during the transition from growth to stationary phase in the vegetative mycelium (Hallam, S.E. *et al.* Gene (1988) 74:305-320).

Type II clusters in *Streptomyces* are known to be activated by pathway-specific activator genes (Narva,

K.E. and Feitelson, J.S. J. Bacteriol. (1990) 172:326-333; Stutzman-Engwall, K.J. *et al.* J. Bacteriol. (1992) 174:144-154; Fernandez-Moreno, M.A. *et al.* Cell (1991) 66:769-780; Takano, E. *et al.* Mol. Microbiol. (1992) 6:2797-2804; Gramajo, H.C. *et al.* Mol. Microbiol. (1993) 7:837-845). The DnrI gene product complements a mutation in the *actII*-orf4 gene of *S. coelicolor*, implying that DnrI and ActII-orf4 proteins act on similar targets. A gene (*srmR*) has been described (EP 0 524 832 A2) that is located near the Type I PKS gene cluster for the macrolide polyketide spiramycin. This gene specifically activates the production of the macrolide antibiotic spiramycin, but no other examples have been found of such a gene. Also, no homologues of the ActII-orf4/DnrI/RedD family of activators have been described that act on Type I PKS genes. WO 98/01546 describes the use of the ActII-orf4 family of activators in conjunction with their cognate promoters (e.g actII-orf4 with the *actI* promoter) in a heterologous actinomycete to obtain high level expression of recombinant Type I polyketide synthase genes.

Although large numbers of therapeutically important polyketides have been identified, there remains a need to obtain novel polyketides that have enhanced properties or possess completely novel bioactivity. The complex

polyketides produced by Type I PKSs are particularly valuable, in that they include compounds with known utility as anthelminthics, insecticides, immunosuppressants, antifungal agents or antibacterial agents. Because of their structural complexity, such novel polyketides are not readily obtainable by total chemical synthesis, nor by chemical modifications of known polyketides.

There is also a need to develop reliable and specific ways of deploying individual genes and portions of genes in practice so that all, or a large fraction, of hybrid PKS genes that are constructed, are viable and produce the desired polyketide product. This includes the development of advantageous host strains for expression of such genes. For example many polyketides are rendered bioactive by the action of further enzymes other than the polyketide synthase, and host strains that contain and are able to express the genes for such enzymes are particularly convenient for the efficient synthesis of the bioactive material. In those cases where the construction of a known or a novel polyketide requires specialised precursors, host strains containing and able to express the genes for key enzymes that enhance the production of such specialised precursors are equally valuable and desirable. There is also a need to develop

rational methods of increasing the expression level of all the genes required for production of a specific polyketide. Clearly also a host cell which is advantageous for the above reasons, and/or because of other favourable characteristics including but not limited to its speed of growth, excellent handling characteristics in fermentation, and ease of transformation with DNA by various techniques, can be made even more favourable by the cloning into that cell of such auxiliary genes for polyketide modification, or gene activation, or post-translational modification, or precursor supply.

The DNA sequences have been disclosed for several Type I PKS gene clusters that govern the production of 16-membered macrolide polyketides, including the tylosin PKS from *Streptomyces fradiae* (application EP 0 791 655 A2), the niddamycin PKS from *Streptomyces caelestis* (Kavakas, S.J. *et al.* J. Bacteriol. (1997) 179:7515-7522) and the spiramycin PKS from *Streptomyces ambofaciens* (application EP 0791 655 A2). DNA sequences have also been disclosed for Type I PKS gene clusters that govern the production of further complex polyketides, for example rifamycin from *Amycolatopsis mediterranei* (WO 98/07868), and soraphen from *Sorangium cellulosum* (US

5716849), but so far no DNA sequence has been disclosed for one of the most widespread and important classes of complex polyketides, the polyethers.

Polyethers form an important group of complex polyketide antibiotics (Westley, J.W. in "Antibiotics IV. Biosynthesis" (Corcoran, J.W. Ed.), Springer-Verlag, New York (1981) p. 41-73). They are polyoxygenated carboxylic acids which act as selective ionophores transporting cations across the cell membrane of target cells and thereby causing depolarisation and cell death. Certain polyethers including monensin, lasalocid and tetronasin are in widespread use in animal husbandry as coccidiostats (principally targetted against *Eimeria spp.*) and as growth promoters. Polyethers have also been reported to be active *in vitro* and *in vivo* against the malarial parasite *Plasmodium falciparum* (Gumila, C. *et al.* Antimicrobial Agents and Chemotherapy (1997) 41: 523-529).

Polyethers contain multiple asymmetric centres and are characterised by the presence of tetrahydrofuran and tetrahydropyran rings, producing a characteristic shape which is non-polar on its outer surface and therefore well adapted for transport of material across bacterial membranes; and provides on its inner surface polar coordinating ligands for a centrally-bound metal ion. In

addition to tetrahydrofuran and tetrahydropyran rings, other groups which are often present include spiroketal, dispiroketal, and substituted benzoic acid moieties and occasionally other groups for example a tetronic acid or a 6-membered carbocyclic ring

Monensins A and B are produced by the actinomycete *Streptomyces cinnamonensis*. Their structures are shown in Figure 1. Monensin B differs from monensin A only in the presence of a methyl sidechain at C-16 rather than an ethyl sidechain. Monensin selectively binds and transports sodium ions. In addition to its antibacterial and antifungal properties monensin has some activity against protozoal parasites such as the malarial parasite *Plasmodium falciparum*. Although the structures of polyethers differ significantly from those of other complex polyketides such as the polyhydroxylated and polyene macrolides, their biosynthesis appears to take place by a metabolic pathway which has many common elements. Thus experiments using carbon 14-labelled precursors have shown that monensin A is synthesised from five acetate, one butyrate and seven propionate units (Day, L.E. *et al.* Antimicrob. Agents Chemother. (1973) 4:410-414). Similarly experiments using precursors doubly-labelled with carbon-13 and oxygen-18 have shown that oxygens (O)1, (O)3, (O)4, (O)5, (O)6 and (O)10 of

monensin arise from the carboxylate oxygens of either propionate or acetate, while growth in the presence of oxygen-18 oxygen gas demonstrated that the three remaining ether oxygens (O)7, (O)8 and (O)9 are derived from molecular oxygen (Cane, D.E. *et al.*, J. Am. Chem. Soc. (1981) 103:5962-5965; Cane, D.E. *et al.* J. Am. Chem. Soc. (1982) 104:7274 - 7281; Ajaz, A.A. and Robinson, J.A. J. Chem. Soc. Chem. Commun. (1983) 12:679-680). These findings have been rationalised by proposing that the biosynthesis of monensin proceeds via an acyclic triene intermediate (1) in which the geometry of all three carbon-carbon double bonds is E (entgegen) rather than Z (zusammen). The triene is then proposed to be subject to epoxidation to a tri-epoxide (2) and then ring opening is proposed to occur with concomitant sequential formation of the five ether rings as shown in Figure 2A. Such a biosynthetic pathway, first mooted by Westley in 1974 (Westley J.W. *et al.*, J. Antibiot. (1974) 27:597-604) accounts for the observed stereochemistry at the multiple asymmetric centres in monensin, (Cane, D.E. *et al.* J. Am. Chem. Soc. (1982) 104:7274-7281; Sood, G.R. *et al.* J. Chem. Soc. Chem. Commun. (1984) 21:1421-1424) and analogous schemes can be used to account for the biosynthesis of other known polyethers. such as lasalocid A (Hutchinson C.R. *et al.*, J. Am. Chem. Soc. (1981)

103:5953-5956), tetronasin (ICI 139603) (Demetriadou, A.K. *et al.* J. Chem. Soc. Chem. Commun. (1985) 7:408-410) and narasin (Spavold, Z. *et al.* Tetrahedron Letters (1986) 27:3299-3302). The hydroxylation at C-26 and the introduction of an O-methyl group on oxygen 3-are proposed to occur as late steps in the biosynthesis, after formation of the polyether structure.

Unfortunately key aspects of the biosynthetic scheme shown in Figure 2A have so far eluded experimental confirmation. No biosynthetic intermediates have been isolated from mutants of *S. cinnamonensis* that are blocked in early stages of monensin production. 26-deoxymonensin A has been isolated from a *S. cinnamonensis* mutant partially blocked in monensin production (Ashworth, D.M. *et al.* J. Antibiot. (1989) 42:1088-1099) and 3-0-demethylmonensins A and B have been recovered as minor components from the fermentation broth of a monensin-producing strain (Pospisil, S. *et al.* J. Antibiot. (1987) 40:555-557). When fed to cells of *S. cinnamonensis* in radio-labelled form, neither 26-deoxymonensin A, nor 3-0-demethylmonensin A, nor 3-0-demethyl, 26-deoxymonensin A were significantly incorporated into monensin A (Ashworth, D.M. *et al.* J. Antibiot. (1989) 42:1088-1099), either because they are actively excluded or because these modifications in fact

occur earlier in the biosynthetic pathway so that these metabolites are shunt products not readily converted into the final antibiotic by the respective hydroxylase or methyltransferase. Similarly, the putative all (E)-triene precursor (1) has been synthesised and shown not to become incorporated into monensin when fed to growing cells of *S. cinnamonensis* (Holmes, D.S. *et al.* Helv. Chim. Acta (1990) 73:239-259). An alternative pathway has been proposed, as shown in Fig 2B, based on the transition-metal-mediated oxidation of 1,5-dienes (Walba, D.M. and Edwards, P.D. Tetrahedron Lett. (1980) 21:3531-3534). The triene intermediate (4) would different from that of Figure 2A (1) only in that each carbon-carbon double bond would have the (Z)-configuration (Townsend, C.A. and Basak, A. Tetrahedron (1991) 47:2591-2602) and not the (E)- configuration.

The genetic basis of secondary metabolite biosynthesis essentially exists in the genes which code for the individual biosynthetic enzymes and in the regulatory elements which control the expression of the biosynthetic genes. The genes encoding biosynthesis of polyketides in actinomycetes have hitherto been found as clusters of adjacent genes, ranging in size from 20 kilobasepairs (kbp) to over 100 kbp. The clusters often contain specific regulatory genes and genes

conferring resistance of the producing strain to its own antibiotic.

In various of its aspects the invention provides the following:-

(1) a DNA sequence encoding at least one-peptide necessary for the biosynthesis of monensin, preferably comprising one or more of the following genes: *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX* as depicted in the appended sequence data or an allele or mutation thereof;

(2) a DNA sequence according to the first aspect comprising all of the genes listed therein or an allele or mutation thereof;

(3) a DNA sequence according to the first aspect comprising the complete monensin gene cluster;

(4) a DNA sequence coding for one or more of the peptides set out below, said peptide having the amino acid sequence as set out in the appended sequence data or being a variant thereof having the specified activity:

<u>peptide</u>	<u>activity</u>
mon CII	epoxyhydrolase/cyclase
mon E	S-adenosylmethionine-dependent methyltransferase
mon T	monensin resistance gene
mon RII	repressor protein
mon AIX	thioesterase

mon AI	polyketide synthase multienzyme
mon AII	polyketide synthase multienzyme
mon AIII	polyketide synthase multienzyme
mon AIV	polyketide synthase multienzyme
mon AVI	polyketide synthase multienzyme
mon AVII	polyketide synthase multienzyme
mon AVIII	polyketide synthase multienzyme
mon H	regulatory protein
mon CI	flavin-dependent epoxidase
mon BII	carbon-carbon double bond isomerase
mon BI	carbon-carbon double bond isomerase
mon D	cytochrome P450 hydroxylase
mon RI	activator protein
mon AX	thioesterase

(5) a recombinant cloning or expression vector comprising a DNA sequence according to any of aspects 1-4;

(6) a transformant host cell which has been transformed to contain a DNA sequence according to any of aspects 1-4 and is capable of expressing a corresponding peptide;

(7) a hybridization probe comprising a polynucleotide which binds specifically to a region of the monensin gene cluster selected from *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX;*

(8) use of a probe according to aspect (7) in a method of detecting the presence of a gene cluster which governs the synthesis of a polyether, and optionally isolating a gene cluster detected thereby;

(9) Use of a probe comprising a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, preferably a regulatory gene, resistance gene or thioesterase gene, more preferably the regulatory gene *mon RI*, in a method of detecting an analogous gene in a gene cluster of another polyketide, preferably a polyether, and optionally manipulating the gene detected thereby to alter the level of expression of said other polyketide;

(10) a host cell, preferably *Streptomyces cinnamonensis*, containing a heterologous gene under the control of the *mon RI* gene and a monensin promoter;

(11) use of a portion of the monensin gene cluster having chain terminating activity, preferably comprising at least one of *mon AIX* and *mon AX* or a mutant or allele thereof having chain terminating activity, to effect chain release of a peptide other than one required for monensin biosynthesis;

(12) use of a portion of the monensin gene cluster having carbon-carbon double bond isomerase activity, preferably comprising at least one of *mon BI* and *mon BII*

or a mutant or allele thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of a polyketide other than monensin;

(13) a polypeptide encoded by a portion of the monensin gene cluster, preferably comprising at least one of *mon BI* and *mon BII* or a mutant or allele thereof, having carbon-carbon double bond isomerase activity;

(14) an epoxidase enzyme encoded by *mon CI* or a derivative or variant thereof having epoxidase activity;

(15) a cyclase enzyme encoded by *mon CII* or a derivative or variant thereof having cyclase activity.

Some embodiments of the invention will now be described by way of example with reference to the accompanying drawings in which:

Fig 1 shows the structure of monensins A and B;

Fig 2 illustrates proposed biosynthetic pathways;

Fig 3 illustrates the proposed organization of the monensin polyketide synthase (PKS) enzyme complex; and

Fig 4 illustrates the proposed organization of the monensin biosynthetic gene cluster.

The overall gene organization of the monensin biosynthetic gene cluster, as shown in Fig 4, is similar to that previously found for many macrolide biosynthetic gene clusters, which have one or more open reading frames (ORFs) encoding large multifunctional PKSs flanked by

other genes which encode functions required for the biosynthesis of the antibiotic. In the case of monensin, there is an unusually high number of distinct ORFs encoding PKS multi-enzymes (eight in total, labelled *monAI* to *monAVIII*) but there is again a separate module of enzymes for each cycle of polyketide chain extension, exactly as found for modular PKSs for macrolide biosynthesis (see Fig 3). Thus there are 12 condensations predicted to be required for the production of the carbon skeleton of monensin, and in agreement with this there are found to be 12 extension modules of PKS enzymes distributed among the 8 PKS ORFs. However, as mentioned in detail below, the other genes in the monensin cluster include genes which have not previously been found in any other gene cluster for the biosynthesis of a complex polyketide, and which are not significantly similar to any genes in published sequence databases. The cloned DNA for these genes is useful to allow the diagnosis that a polyketide biosynthetic gene cluster in any actinomycete, uncovered previously by conventional hybridization against a PKS gene probe from (say) the DEBS or some other characterised PKS gene cluster, is one that governs the synthesis of a polyether; and these genes are also valuable either singly or in combination as specific hybridization probes for the specific detection and

isolation of additional polyether biosynthetic gene clusters. Examples of these previously-unknown genes are the genes *monBI*, *monBII*, *monCI* and *monCII*. In addition the regulatory genes *monH* *monRI*, and *monRII* and the resistance gene *monT* and the thioesterase genes *monAIX* and *monAX* are all useful for the detection of analogous genes in other polyether clusters which are required for the rational manipulation of such genes in order to increase levels of the specific product.

The cloned and sequenced cluster of genes for monensin biosynthesis is useful secondly in the engineering of mutant strains of *S. cinnamonensis* and of other actinomycetes which are suitable strains for the high level production of either natural or novel recombinant polyketides. The sequence of the monensin cluster disclosed here shows the surprising fact, that the gene cluster contains a gene *monRI* whose gene product has an amino acid sequence highly similar to that of *actII*-orf4, the pathway-specific activator gene which activates the *actI* and other promoters of the actinorhodin biosynthetic gene cluster of *Streptomyces coelicolor*. The recognition of this aspect of the natural regulation of a Type I PKS cluster is important and valuable because first, it is possible to increase the yield of monensin by increasing the level of the activator MonRI, either by

placing the gene *monRI* under the control of a powerful promoter or arranging for the presence within the cells of one or more additional copies of the *monRI* gene (as exemplified below); secondly, it will be possible to use the *monRI* gene as a specific hybridisation probe to locate similar genes in other complex PKS gene clusters, especially other polyether PKS gene clusters but also polyene and macrolide gene clusters and all other Type I modular PKS gene clusters; even in cases where (as for rapamycin and erythromycin) no such gene has been previously found within the currently accepted physical limits of the relevant biosynthetic gene cluster. In such cases the *monRI* gene probe might be expected to uncover the activator even if it resides on the chromosome at some distance from the main body of the gene cluster; and simple experiments would then show whether the activator(s) so uncovered are involved in regulation of the biosynthesis of those particular metabolites; thirdly, increasing the copy number of the *monRI* gene or of any of the activator genes uncovered will tend to increase the yield of a heterologous polyketide by "crosstalk" where the activator mimics the presence of the normal activator for the transcription of the genes for that heterologous polyketide synthase. It is clear from recently published work (Wietzorrek, A. and Bibb, M. Mol. Microbiol. (1997)

25:1181-1184) that the ActII-orf4 family of activators exert their effects by binding to promoter regions within the target gene cluster, so it will be possible to use the *monRI* gene together with monensin promoter regions to drive the high-level transcription and translation of heterologous genes in *Streptomyces cinnamonensis*, and perhaps in other host strains too; such genes need not be PKS genes or even involved in polyketide biosynthesis. Monensin promoter regions are found at the 5′ end of genes or groups of genes in the cluster and their location is clear from the sequence analysis disclosed here. Thus a useful vector would provide the monensin promoter and the ribosome binding site and continue up to the start of the open reading frame, after which the monensin ORF naturally found there would be replaced by the heterologous gene. The relative strength of the monensin promoters can be readily determined using any one of a number of known promoter probes, i.e. genes whose expression gives rise to readily measurable and quantifiable effects, such as Green Fluorescent Protein (GFP); or beta-galactosidase in the presence of a chromogenic substrate. It should be possible to mutate randomly the small region of the monensin promoters especially likely to interact with the MonRI activator (identified by the presence of tandem heptanucleotide repeats with a common consensus sequence

between the various monensin promoters) (Wietzorrek, A. and Bibb, M. Mol. Microbiol. (1997) 25:1181-1184), and to determine the optimal DNA sequence for the maximal activation effect using either *S. cinnamonensis* (preferably - in case there are other unknown factors that make the activation function better in this strain than in other heterologous systems), or even in another host actinomycete strain. If the natural monensin promoters were mutated to have this optimal recognition sequence, then this would further increase the production of monensin. By extension, the use of this modified monensin promoter in conjunction with the *monRI* gene in heterologous systems could form the basis of further improvements in expression of polyketide synthases or other genes, either by appropriate chromosomal alterations to introduce the altered promoter and also the *monRI* gene; or by provision of vectors containing these optimised signals linked to specific genes and housed in suitable host cells.

The sequencing of the monensin cluster has uncovered another strategy for gene regulation in such Type I clusters. The previously-sequenced genes for the rapamycin biosynthetic pathway in *Streptomyces hygroscopicus* included a gene of unknown function (*rapH*). A closely similar gene has now been found in the monensin

biosynthetic gene cluster (*monH*), and it is clear from this recurrence (and the comparison of the sequences with those of database proteins) that this gene is potentially an important DNA-binding sensor gene which acts to regulate the transcription of the cluster in concert with other regulatory signals. Simple experimentation is needed in order to define whether the gene is an activator, in which case putting in another copy or increasing its transcription will have the potential to increase polyketide biosynthesis; or alternatively the *rapH* gene product may be a negative regulator, whereupon deletion of this gene may release the biosynthetic pathway from this inhibitory effect and increase yields.

There is a continuing need to develop new methods of high-level production of bioactive metabolites and other valuable gene products in actinomycetes. *Streptomyces cinnamonensis* is a recognised and very valuable industrial strain for the production of very high levels of monensin, it is readily transformable with DNA by standard methods of conjugation or of protoplast transformation, it is a host for numerous known broad range plasmids including well-known expression plasmids of both high- and low-copy number, it also grows quickly relative to other actinomycete strains (for example about three times faster than wild type *Saccharopolyspora erythraea* the

erythromycin producer, under comparable conditions) and sporulates relatively easily. Heterologous polyketides can be expressed in *Streptomyces cinnamonensis* using for example the low-copy number plasmid pCJR24 (which has no origin of replication active in actinomycetes so is maintained by integration into the chromosome) (Rowe, C. *et al.* Gene (1998) 216:215-223) or the related plasmid pCJR29 in which the polyketide synthase gene(s) are placed under the control of the *actI* promoter which is activated by the ActII-orf4 activator; or alternatively the *monAI* promoter can be substituted together with the MonRI activator; or some other pairing of activator and cognate promoter chosen from either a Type II or a Type I polyketide synthase gene cluster. As an example, the wild type strain of *Streptomyces cinnamonensis* has been used to express the plasmid pCJR29 (Rowe, C. *et al.* Gene (1998) 216:215-223) containing as insert the three ORFs for the PKS governing the production of 6-deoxyerythronolide B, the macrolide precursor of erythromycin A in *Saccharopolyspora erythraea*, these genes being placed under the control of the pathway-specific *actI* promoter from *Streptomyces coelicolor* together with its cognate activator gene *actII*-orf4. The transformed strain when cultivated in a suitable liquid medium produced 6-deoxyerythronolide B in good yield.

It is well known to the person skilled in the art that it is possible to use standard vectors unable to replicate in actinomycetes to introduce DNA into a *Streptomyces* cell, such DNA comprising two portions of contiguous DNA which are each identical to one of two portions of the cell's chromosome that are spaced up to 100 kbp apart; and that through recombination between the incoming DNA and the chromosome occurring in both portions of DNA the net result is that the chromosomal sequence is replaced by the defective sequence originally that of the incoming DNA. Such a procedure has been applied to the monensin-producing strain of *S. cinnamonensis* as described in detail below, and a strain of *S. cinnamonensis* has been obtained that carries a specific deletion in the monensin cluster and which is unable to produce the antibiotic. The use of such a strain facilitates the production of heterologous polyketides by removal of the background of monensin production.

The multiple uses of portions of the cloned and sequenced DNA from the monensin cluster will readily occur to the person skilled in the art. A surprising feature of the PKS of the monensin cluster is an unusual mechanism of polyketide chain initiation. We have found that the monensin PKS loading module has three domains, which from the amino-terminus of the protein are: a KSq domain, an

acyltransferase domain and an ACP domain. We have uncovered this organisation in the PKS for the 14-membered macrolide oleandomycin as well as in the monensin PKS, an organisation of the loading module previously only found for the 16-membered macrolides and in which the KSq domain (which looks like a ketosynthase or condensation domain except that the active site cysteine residue is substituted by a glutamine for which the single letter notation is Q) had been previously speculated to have no function. It was realised that the acyltransferase of the loading module actually has malonyl-CoA and not acetyl-CoA as a substrate and that KSq is an active decarboxylase. It appears that a better discrimination can be achieved in the selection of the smaller acetate unit over propionate if the choice is made initially between methylmalonyl- and malonyl-CoA.

An unprecedented feature of the monensin PKS genes is that no integral chain-terminating domain is present as a C-terminal appendage of the PKS extension module that catalyzes the twelfth and final chain extension. Because the product of the monensin PKS is a carboxylic acid, it would have been firmly predicted that chain release would have been catalyzed by such a C-terminal domain containing a "thioesterase" activity. Previously sequenced PKS gene sets have been of two sorts: first, those macrolide PKSs

typified by erythromycin, spiramycin, tylosin, niddamycin which have a readily recognisable C-terminal "thioesterase" domain, which in these enzymes functions as a specific cyclase rather than releasing the polyketide product as a free carboxylic acid; secondly, those macrolide PKSs typified by rapamycin, FK506, and rifamycin, where there is an alternative and recognised mode of chain termination by transfer of the polyketide chain to an acceptor moiety, catalyzed by a specific enzyme (eg pipecolate incorporating enzyme for rapamycin (Schwecke T. *et al.* Proc. Natl. Acad. Sci. USA (1995) 92:7839-7843) and FK506 (Mothamedi H. and Shafiee A, Eur. J. Biochemistry (1998) 256:528-534); arylamine synthetase for rifamycin (August P.R. *et al.* Chemistry & Biology (1998) 5:69-79).

The monensin PKS surprisingly falls into neither category, and therefore seems to be the first example of a novel mode of chain termination. It is novel and noteworthy in this connection that the monensin PKS gene cluster contains two small genes that encode discrete, monofunctional thioesterase enzymes. Although many PKS gene clusters have been previously shown to contain one such discrete thioesterase, none have been shown to have two. The role of such thioesterases is not known, although in the case of methymycin/pikromycin PKS, which has been

reported to be responsible for the biosynthesis of both the 12-membered macrolide methymycin and the 14-membered macrolide pikromycin (Xue Y.Q. Proc. Natl. Acad. Sci. USA (1998) 95:12111-12116) the disruption of this thioesterase reportedly caused a ten-fold drop in the amount of both macrolides produced. A similar finding has been reported for the discrete thioesterase of the tylosin PKS gene cluster (Cundliffe E. *et al.* Chemistry & Biology in press). Additional copies of such thioesterases may therefore accelerate the production of specific polyketide, but this has not yet been demonstrated. However, the presence of the discrete thioesterase is not completely essential for polyketide production.

It is highly desirable to have a broadly effective method of catalysing the release of polyketide gene products from a PKS as the free acid. The well-studied integral thioesterase domain in the erythromycin PKS thioesterase has a broad specificity in cyclization to form a lactone (assuming that a hydroxy group is present in the growing polyketide chain at an appropriate position), but hydrolysis to form the free acid is very slow. The recognition of the unusual arrangement of the monensin PKS means that it is now possible to harness either the entire PKS module that catalyses the twelfth and final extension cycle in monensin biosynthesis, or the

C-terminal portion of it, and graft it onto a different polyketide synthase by genetic engineering, so as to allow the release mechanism characteristic of monensin to operate in a different context. The use of this portion only of the monensin PKS suffices to allow the novel mechanism of chain release to operate successfully. The speed of the polyketide chain hydrolysis in a given case can depend on the additional presence of one or both of the discrete thioesterase genes (*monAIX* and *monAX*) from the monensin gene cluster. The use of this novel method of chain termination represents a valuable way of generating a large number of novel engineered polyketides that are currently inaccessible, and ensuring that the products have a specified chain length.

The genes *monBI* and *monBII* appear to encode very similar enzymes with significant amino acid sequence similarity to authentic ketosteroid isomerases which are known to catalyse the migration of an activated carbon-carbon double bond. The conservation of active site residues makes it very likely that these *mon* genes govern a reaction involving activated double bonds in the biosynthetic pathway to monensin and this surprising observation can be accommodated if the initial product of the polyketide chain growth on the monensin PKS is a linear precursor in which the double bonds were initially

formed with a conventional *trans* or E (entgegen) geometry; but before the polyketide chain was extended by insertion of the next unit the *monBI* and/or the *monBII* gene product(s) catalyse the specific rearrangement of the newly-created double bond into the *cis* or Z (zusammen) geometry. This new view of the monensin biosynthetic pathway allows the deduction that the *monBI* and *monBII* genes, perhaps in combination with specific portions of the monensin modules where they normally exert their effects (namely modules 3, 5 and 7) might be used in order to achieve the extremely desirable targetted biosynthesis of novel polyketides containing double bonds with Z geometry at specified point(s) along the chain. Thus for example it should be possible to provide for the direct biosynthesis of C22-C23 *cis* or Z double bond in avermectins, thus avoiding tedious and expensive chemical conversion of an initial fermentation product into this important anthelminthic. Only limited experimentation is needed to see whether the *monBI* and/or *monBII* gene products are sufficient or whether the *mon* PKS at modules 3, 5 and 7 forms part of the specific docking site(s) for the isomerases and therefore must also be used in the creation of the hybrid PKS that will insert the *cis* or Z double bond at the desired position. The substrate specificity of the isomerases need not be limited to 2,3-

unsaturated thioesters. The purified enzymes could also be used to effect such isomerisations *in vitro*, depending on the position of the equilibrium or whether further enzymes are used to achieve the further transformation of the product as it is formed (*vide infra*).

The product of the *monCI* gene is a novel oxidative enzyme with some sequence similarity to authentic examples of such enzymes in the databases; and with a clearly definable role in the monensin biosynthetic pathway, the epoxidation of the double bonds at three separate positions in the initially-formed acyclic intermediate in monensin biosynthesis. This epoxidase could therefore be used in conjunction with *monBI/monBII* gene products to effect oxidative reactions on suitable substrates *in vitro* and *in vivo*. Similarly the *monCII* gene product is a putative cyclase that opens the epoxides and causes the formation of ether rings in monensin.

Any or all of the *monBI, monBII, monCI or monCII* genes may be introduced into a heterologous strain containing the gene cluster for another polyether, in order to divert the biosynthetic pathway and produce a polyketide of altered structure. In these experiments the analogues of these *monB* genes could either be present or (once located and characterised using the *mon* genes as probes) they may be deleted prior to the introduction of

the *monB* and *monC* genes into that strain. The converse experiment in which analogues of the *monB* and *monC* genes from other strains are introduced into *S. cinnamonensis* likewise has the potential to produce novel oxidised polyketides. Also, the *monB* and *monC* genes or their analogues may be introduced into a strain that normally produces a macrolide or a polyene or some other complex polyketide and expressed there, when they may effect the diversion of the growing polyketide chain on a heterologous modular PKS towards a new product, which may or may not have the structure of a polyether.

The availability of the monensin gene sequence allows the institution of domain swaps to alter the acyltransferase (AT) specificity of a given module, for example the ethylmalonyl-CoA specific extender found in one of the modules of the monensin PKS can be used to replace one of the other ATs to generate an ethyl side branch at that position in the chain, or the AT can be used to substitute in any other (e.g. macrolide) PKS, as described in WO 98/01571 and WO 98/01546. Similarly the alteration of the level of reduction in a module, by manipulation of the reductive enzymes, can be applied to the monensin genes and here it will produce, depending on which module is affected, either an altered monensin, or a

species which is only partly cyclised, or a polyether with an altered pattern of cyclisation, or even a linear polyketide.

In general the targetted alteration of the pattern of substitution of sidechains or reduction level along the polyketide chain produced by the monensin PKS will, like the disruption or deletion of the oxidative enzymes mentioned above, lead to non-polyether polyketide products. It should be possible, by introduction of the DEBS thioesterase at the C-terminus of one of the later modules of the monensin PKS, together with an appropriately placed hydroxy group earlier in the chain, to produce novel macrolide products from this polyether PKS system, or alternatively novel polyenes of defined chain length and chosen ring size.

Example 1

Cloning of the monensin A biosynthetic gene cluster using DNA probes derived from the erythromycin-producing polyketide synthase of *Saccharopolyspora erythraea*

A genomic library of the monensin A producing strain *Streptomyces cinnamonensis* ATCC 15413 was constructed using methods well-known in the art, namely, the production of high molecular weight genomic DNA, followed by the partial cleavage of this DNA using the frequent-cutting restriction enzyme *Sau*3A, fractionation of the fragments on a sucrose gradient and selection of fragments of average size 35-40 kbp, and the cloning of these fragments into the cosmid vector pWE15 (Evans, G.A. *et al.* Gene (1989) 79:9-20) which had been previously digested with *Bam*HI and treated with shrimp alkaline phosphatase. The library was packaged and transfected into *Escherichia coli* XL-1 Blue MR cells. The library was plated out on 2xTY agar medium (10 g tryptone, 10 g yeast extract, 5 g NaCl, 15 g bactoagar per litre containing ampicillin 50 μg/ml) for cosmid selection and the colonies were allowed to grow overnight. The library was then screened by hybridisation using as a probe DNA encoding the ketosynthase domain of module 1 of the erythromycin-producing PKS (6-deoxyerythronolide B synthase, DEBS) of *Saccharopolyspora erythraea*. The colonies giving a

positive hybridisation signal in the hybridisation were selected and the cosmid DNA from each colony was purified and mapped by restriction digestion. The presence of the target biosynthetic genes on a cosmid was verified by sequencing of the ends of the cosmid inserts using the commercially available T3 and T7 primers which hybridise specifically to the respective ends of each cosmid insert (Evans, G.A. *et al.* Gene (1989) 79:9-20).

Example 2

Sequencing of the biosynthetic gene cluster for monensin A from *Streptomyces cinnamonensis*

Three cosmids obtained by screening of the genomic library of *S. cinnamonensis* were used to obtain the entire DNA sequence of the monensin biosynthetic gene cluster. These cosmids, MO.CN02, MO.CN11 and MO.CN33 between them contain the entire DNA sequence of the cluster and the adjacent regions of the chromosome. They have been deposited in NCIMB, 23 St Machair Drive, Aberdeen AB24 3RY, UK, under the NCIMB accession numbers 40956 (MO-CN11); 40957 (MO-CN33) and 40958 (MO-CN02) respectively.

The DNA of each cosmid was separately subjected to partial digestion with *Sau*3A and fragments of approximately 1.5-2.0 kbp were separated by agarose gel electrophoresis. The fragments were then ligated into the

plasmid vector pUC18 (Messing, 1982), previously digested with *BamHI* and treated with shrimp alkaline phosphatase. The library was transformed into *E. coli* strain XL1-Blue MR and plated on 2xTY agar medium containing ampicillin (100 µg/ml) to select for plasmid-containing cells. Plasmid DNA was purified from individual colonies and sequenced using the Sanger dye-terminator procedure on an ABI 377 automated sequencer (Sanger, F. Science (1981) 214:1205-1210). The sequence data obtained from single random subclones of a cosmid was assembled into a single continuous sequence and edited using GAP4.1 program of the STADEN gene analysis package (Staden, R. Molecular Biotechnology (1996) 5:233-241).

The sequence is set out in the appended sequence listing.

Tables I and II contain data about individual genes and gene products.

Example 3

Inactivation of the monensin A biosynthetic gene cluster

A chromosomal gene disruption experiment was used to verify the identity of the cloned polyketide synthase gene cluster. Plasmid pMOB6314 is a pUC18 sequencing subclone of the presumed monensin A biosynthetic gene cluster prepared as described in Example 1, whose inserted DNA comprises the DNA sequence from nucleotide 9763 to

nucleotide 10108 in SEQ ID 1, and which therefore contains a region of DNA wholly internal to *orfE*, a putative 3-O-methyltransferase. A *Hin*dIII fragment containing the thiostrepton resistance gene *tsr* from plasmid pIJ702 (Katz, E. *et al.* J. Gen. Microbiol. (1983) 129:2703-2714) was cloned into the *Hin*dIII site of plasmid pMOB6314 and the ligation mixture was used to transform *E. coli* cells. Transformants bearing the required plasmid pMOΔE01 were identified by isolation of plasmid DNA and analysis by restriction digestion. pMOΔE01. Plasmid pMOΔE01 was used to transform protoplasts of *Streptomyces cinnamonensis* as described by (Hopwood D.A. *et al.* (1985)). Since plasmid pMOΔE01 lacks an origin of replication that is active in *Streptomyces*, growth in the presence of thiostrepton (25 µg/ml) in the regeneration medium led to the isolation of stable integrants. Isolated putative integrants were tested for the presence of integrated pMOΔE01 sequences by Southern hybridisation. A clone of *Streptomyces cinnamonensis* identified by its restriction pattern in Southern hybridisation as bearing pMOΔE01 integrated in the region of *monE* of the monensin A biosynthetic gene cluster was designated *S. cinnamonensis* MO-DD01.

Detection of production of the monensin A related metabolites produced by *S. cinnamonensis* MO-DD01 was performed by GC-MS analysis of methanol extracts of the

entire broth harvested in 72 hours of growth of the strain. No significant amounts of monensin A-related metabolite production were detectable.

Example 4

Overproduction of erythromycin aglycone in *Streptomyces cinnamonensis*

S. cinnamonensis is a suitable system for overproduction not just of monensin A but also of other polyketide metabolites. Established techniques of genetic transformation allow fast introduction of foreign polyketide producing genes sets into this host. Fast growth of *S. cinnamonensis* in liquid culture and optimal precursor supply favour high yield of polyketide metabolites.

Construction of pIB061

S. erythraea NRRL2338 was transformed with pCJR30 (Rowe, C. J., et al. (1998) Gene 216:215-223) using a routine protoplast transformation technique as described by Hopwood et al. (1985). A stable integrant of *S. erythraea* [pCJR30] was identified and the production of 10mg/L of the triketide lactone (delta lactone of (2S,3R,4R,5R)-2,4-dimethyl-3,5-dihydroxy-heptanoic acid) in addition to erythromycins was confirmed by MS analysis.

Total DNA of *S. erythraea* [pCJR30] was purified and

approximately 200 ng was digested with *Eco*RI endonuclease. The digestion mixture was precipitated with isopropanol and the resulting DNA was treated with T4 DNA-ligase for 16 hours at 16°C. The ligation mixture was used to transform *E.coli* DH10B cells. The transformants were screened for the presence of the plasmid. A clone containing a 44.7kb plasmid was identified and confirmed by restriction analysis to contain three complete genes: *ery*AI, *ery*AII and *ery*AIII. The plasmid was named pIB061.

Transformation of *S. cinnamonensis*

Protoplasts of *S. cinnamonensis* were prepared by a modified procedure of Hopwood *et al.* (1985). Plasmid pIB061 was transformed into the protoplasts of *S. cinnamonensis* and stable thiostrepton resistant colonies were isolated. Individual colonies were checked for their plasmid content and the presence of plasmid pIB061 was confirmed by its restriction pattern. *S. cinnamonensis* (pIB061) was inoculated into 250 ml of M-C3 minimal production medium containing 10 μg/ml of thiostrepton and allowed to grow for 72 hours at 30 °C. After this time the mycelia were removed by filtering. The broth was extracted with two volumes of ethyl acetate and the combined ethyl acetate extracts were washed with an equal volume of saturated sodium chloride, dried over anhydrous sodium sulphate, and the ethyl acetate was removed under reduced

pressure to give about 200 mg of crude product. The product was analysed by LCQ and mass was confirmed to that of erythronolide B.

This example demonstrates the importance of *S. cinnamonensis* for production of high levels of foreign polyketide antibiotics. Introduction of the complete erythromycin gene cluster or other gene clusters into this system are likely to produce high levels of the corresponding metabolites.

Example 5

Construction of plasmid pCJW58 containing the monensin activator gene under the ermE* promoter

The ermE* promoter derived from the *ermE* resistance methyltransferase gene of *S. erythraea* (Bibb *et al.* Gene (1985) 38:215-226) was amplified by PCR as a *Spe*I-*Xba*I fragment using the following oligonucleotides 5'-CCACTAGTATGCATGCGAGTGTCCGTTCGAGT-3' and 5'-TTGTATACACCTAGGATGGTTGGCCGTGC-3' with pRH3 (Dhillon *et al.* Molecular Microbiology (1989) 3:1405-1414 as a template and cloned into *Sma*I-digested, phosphatase-treated pUC18, to produce plasmid pIB135. The integrative plasmid pSET152 (Bierman, M. *et al.* (1992) Gene 116:43-49)) was digested with *Xba*I and the backbone was dephosphorylated and ligated to the *Spe*I-*Xba*I fragment of pIB135 containing the *ermE** promoter. The ligation mixture was used to

transform *E. coli* DH10B and the orientation of the insert in the plasmids from individual clones was checked by using restriction analysis. A plasmid with the *erm*E* promoter oriented so that the *Nde*I and *Xba*I sites are adjacent to the apramycin resistance gene was selected and named pIB139.

The *monR* gene from the monensin biosynthetic gene cluster was amplified and *Nde*I and *Xba*I restriction sites introduced at 5′ and 3′ ends respectively, by PCR using as primers the following oligonucleotides:
5′-AGA TAC CAT ATG CTG GGC CCG CTC CGC AT -3′
and 5′-AAT GCT CTA GAC TGT CAG CGA CCG GAC AGG GCC AA-3′
and cosmid MO.CN11 as template. The PCR product was ligated into *Sma*I-treated and phosphatase-treated plasmid pUC18 and the ligation mixture was used to transform *E. coli* DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained the *monR* gene flanked by *Nde*I and *Xba*I restriction sites was selected and designated pCJW57.

Plasmid pCJW57 was digested with *Nde*I and *Xba*I and the fragment containing the monR gene was ligated together with the backbone of plasmid pIB139 which had been digested with the same two restriction enzymes, and purified by gel elution. The ligation mixture was used to

transform *E. coli* strain DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by restriction analysis. One such recombinant was selected and named plasmid pCJW58.

Plasmid pCJW58 was used to transform the methylation-deficient *E. coli* strain ET 12567 (MacNeil D. J. et al. (1992) Gene 111:61-68) and the recovered, unmethylated plasmid was then used to transform the same *E. coli* strain ET12567 housing the plasmid pUB307, a derivative of RP4 which is *mob*$^-$ and which contains a gene for kanamycin resistance (Piffaretti, J. C. et al. (1988) Mol. Gen. Genet. 212:215-218). Recombinants were plated on 2 x TY agar medium containing apramycin and kanamycin at final concentrations of 50 micrograms per ml and 50 micrograms per ml respectively. The plasmid content of recombinants was checked isolation of plasmid DNA and checking of the identity of these plasmids by restriction analysis. One such clone which contained both pUB307 and plasmid pCJW58 was selected and used for further experiments.

Construction of *Streptomyces cinnamonensis* (pCJW58) and production of monensins

A single colony of *E. coli* ET12567 housing both pUB307 and pCJW58 was toothpicked into 3 ml of TY liquid medium, containing apramycin and kanamycin at 25 and 25

micrograms respectively, and grown overnight at 37°C. This culture was used to inoculate 25 ml of TY medium, supplemented with the same antibiotics at the same concentrations, and growth was continued until the absorbance at 600 nm (1 cm pathlength) was between 0.3-0.6. The cells were centrifuged (room temperature, 7 minutes, 2000 x *g*), resuspended in TY liquid medium (10 ml) containing no added antibiotics, re-centrifuged as before, then resuspended in 2ml of TSB medium and placed on ice. Meanwhile, 0.5 ml of TSB medium was added to 100 microL containing approximately 10^8 spores of *S. cinnamonensis*. After a brief heat shock, at 50°C for 10 minutes, the suspension was briefly cooled, mixed with 0.5 ml of donor *E. coli* cells, and plated on solid A medium, which has composition as follows:

<u>A medium</u>

Sigma wheat starch	5g
Corn steep powder	1.25g
Yeast extract	1.5g
$CaCO_3$	1.5g
$FeSO_4$	6 mg
DIFCO agar	10g
H_2O	to 500 ml

pH adjusted to pH 7 with KOH.

And to which in addition was added 10 mM $MgCl_2$ to a final concentration of 10 mM.

The plates were allowed to dry overnight at room temperature, and were then allowed to incubate a further 18 hours at 30°C. After this time each 25 ml plate was overlaid with a solution of apramycin (final concentration 50 micrograms per ml) and nalidixic acid (final concentration 20 micrograms per ml), and the plates were allowed to incubate for four days at 30°C. At this time individual colonies were toothpicked onto solid A medium and allowed to grow. Four representative colonies from the A medium plate were grown up in liquid modified YEME medium, which has composition as follows:

<u>Modified YEME medium</u>

Sucrose	100g
DIFCO Yeast extract	3g
Bacto peptone	5g
Oxoid Malt extract	3g
Glucose	10g

H_2O to 1L

pH adjusted to pH 7.2 with NaOH.

These cultures were used to provide a 2% vol/vol inoculum for 30 ml of modified YEME which was grown for 7 days, and then transferred to SM16 medium, which has

composition as follows:

<u>SM16 medium</u>

3-[N-Morpholino]-propane sulfonic acid (MOPS) buffer	20.9g
L-proline	10.0g
Glucose	20g
NaCl	0.5g
K_2HPO_4	2.1g
Ethylenediaminetetraacetic acid, sodium salt	0.25g
$MgSO_4.7H_2O$	0.49g
$CaCl_2.2H_2O$	0.029g
Trace elements solution (Hopwood, D. A. et al. (1985) Genetic Manipulation of *Streptomyces* - a Laboratory Manual, at p.235)	2 ml
0.5 M $CoCl_2$ solution	2 microlitres
H_2O to 1L	

pH adjusted to pH 7 with NaOH.

After growth for a further 7 days, mycelium was collected by centrifugation at 2000 x g for 30 minutes, and the supernatant was extracted three times with 300 ml of ethyl acetate. The combined extracts were concentrated by evaporation under reduced pressure to an oil, which was

mixed with 1 ml of methanol. Samples were applied to an LCQ liquid chromatograph fitted with a mass spectrometer detector unit. The column used was a C18 reversed phase column, equilibrated with a mixture of 80% 20mM ammonium acetate/20% acetonitrile, and the column was eluted with a gradient of increasing acetonitrile, reaching 100% acetonitrile over 24 minutes. Monensins A and B emerged from the column with retention times respectively of 8.2 minutes and 9.2 minutes. The relative amounts of monensin produced by three independent clones (A-C) containing an additional copy of the *monR* gene were compared to a control fermentation of the wild type *S. cinnamonensis* strain, with the results shown in the Table below:

Table showing increased monensin production in strains bearing additional copy of *monR* gene

Strain	monensin A concentration (arbitrary units)	monensin B concentration (arbitrary units)
Control	188	861
A	430	1 800
B	450	1 300
C	249	1 300

Example 6

Construction of *S. cinnamonensis* M12AT5

A region lying immediately 5′ of the DNA encoding the

acyltransferase (AT12) domain of module 12 of the monensin polyketide synthase in the monensin biosynthetic gene cluster was amplified with the following primers: 5′-GGTGGCCACGGAAACACCAACACCGGACCCGCGCC-3′, and 5′-CTCTCGGAGGCCCGGCGCAACGGCCACAA-3′, 3′ using cosmid MO-CN11 as a template. The PCR product was ligated into *Sma*I digested and phosphatase-treated plasmid pUC18 and the ligation mixture was used to transform *E. coli* DH10B cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained a fragment upstream of the AT12-encoding sequence from about 82.3kb to 83.2kb of the *mon* cluster was designated pMO81. Similarly a region lying immediately 3′ of the DNA encoding the acyltransferase (AT12) domain of module 12 of the monensin polyketide synthase in the monensin biosynthetic gene cluster was amplified with the following primers: 5′-GGCCTAGGGCTGCCTCGGGTGGTGGATCTGCCGA-3′ and 5′- TGGTCGGGCGCGGTGCGTGCGATACGT-3′, using cosmid MO-CN11 as a template. The PCR product was ligated into *Sma*I-treated and dephosphorylated pUC18 and the ligation mixture was used to transform DH10B *E.coli* cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert contained

a fragment downstream of the AT12-encoding sequence, from 80.5kb to 81.4kb of the *mon* cluster, was designated pMO82.

The DNA encoding AT of module 5 was amplified and *Msc*I and *Avr*II restriction enzyme recognition sites were introduced at the ends by PCR using the following primers: 5′-CCTGGCCAGGGCGGCCAGTGGGTGGGCATG-3′ and 5′-GGCCTAGGGGTCGGCCGGGAACCAGCGCCGCCAGT-3′ and the cosmid MO-CN33 as a template. The PCR product was ligated into *Sma*I-treated and dephosphorylated pUC18 and the ligation mixture was used to transform DH10B *E.coli* cells. Transformant colonies were analysed for the presence of plasmid and the identity of the plasmid inserts was verified by sequencing. A plasmid whose insert DNA, with sequence from about 44.2kb to 45.2kb of the *mon* cluster, encoded the AT5 domain was designated pMO83.

pMO81 was digested with *Msc*I and *Hin*dIII and ligated to the 0.9kb *Msc*I - *Hin*dIII fragment of pMO82. A clone containing both fragments was designated pMO84. Plasmid pMO84 was cleaved with *Avr*II and *Hin*dIII, treated with phosphatase, and ligated together with the 1.0 kb *Avr*II - *Hin*dIII fragment of pMO83 to produce pMO85, which contains the DNA encoding the AT5 domain flanked by DNA from either side of the DNA encoding the AT12 domain of the monensin PKS. The thiostrepton resistance gene *tsr*, derived from plasmid pIJ702 (Katz, E. et al., J. Gen. Microbiol.

1983), was cloned into the *Hin*dIII site of pMO85. The resulting plasmid pMO86 was analysed by its restriction pattern and confirmed to contain all the desired elements.

Plasmid pMO86 was used to transform *S. cinnamonensis* protoplasts as described by Hopwood, D. A. (1985). Stable thiostrepton-resistant transformants were isolated and checked for the desired integration of the pMO85 into the AT12 flanking regions by Southern blot hybridisation. One such integrant, *S. cinnamonensis* MO-08, containing pMO85 integrated upstream of the AT12, was passed through 4 cycles of sporulation on a non-selective nutrient medium. Spores obtained after the fourth cycle were replica-plated onto media with and without thiostrepton. DNA of clones that had lost thiostrepton resistance was analysed by Southern blot hybridisation. Clones in which the DNA encoding the AT12 domain had been replace by the DNA encoding the AT5 domain was designated *S. cinnamonensis* M12-AT5. At this time individual colonies were toothpicked onto solid A medium and allowed to grow. Four representative colonies from the A medium plate were grown up in liquid modified YEME medium, which has composition as follows:

<u>Modified YEME medium</u>

Sucrose	100g
DIFCO Yeast extract	3g
Bacto peptone	5g
Oxoid Malt extract	3g
Glucose	10g

H_2O to 1L

pH adjusted to pH 7.2 with NaOH.

These cultures were used to provide a 2% vol/vol inoculum for 30 ml of modified YEME which was grown for 7 days, and then transferred to SM16 medium, which has composition as follows:

SM16 medium

3-[N-Morpholino]-propane sulfonic acid (MOPS) buffer	20.9g
L-proline	10.0g
Glucose	20g
NaCl	0.5g
K_2HPO_4	2.1g
Ethylenediaminetetraacetic acid, sodium salt	0.25g
$MgSO_4.7H_2O$	0.49g
$CaCl_2.2H_2O$	0.029g
Trace elements solution (Hopwood, D. A. et al. (1985) Genetic	

Manipulation of *Streptomyces* - a Laboratory Manual, at p.235)	2 ml
0.5 M $CoCl_2$ solution	2 microlitres
H_2O to 1L	

pH adjusted to pH 7 with NaOH.

After growth for a further 7 days, mycelium was collected by centrifugation at 2000 x g for 30 minutes, and the supernatant was extracted three times with 300 ml of ethyl acetate. To confirm presence of the C-2-ethyl substituents of both monensin A and B the combined extracts were concentrated by evaporation under reduced pressure to an oil, which was mixed with 1 ml of methanol. Samples were applied to an LCQ liquid chromatograph fitted with a mass spectrometer detector unit. The column used was a C18 reversed phase column, equilibrated with a mixture of 80% 20mM ammonium acetate/20% acetonitrile, and the column was eluted with a gradient of increasing acetonitrile, reaching 100% acetonitrile over 24 minutes. Mass ions 14 mass units above those expected for both monensin A and B confirmed production of the respective C-2-ethyl substituents.

Example 7. Construction of pSGK005 and its use in the production of C-13 propyl-erythromycin

Plasmid pSGK005 is a pCJR24 based plasmid containing a PKS gene comprising a loading module plus the first and

second extension modules and the chain terminating thioesterase of the PKS responsible for the production of erythromycin (DEBS). The loading module comprises the KS and ethyl-malonyl CoA specific AT from module 5 of the monensin PKS linked to the DEBS loading ACP domain. In addition, the active site cysteine of this module 5 KS has been mutated to glutamine to convert an extender di-domain to a loading di-domain. Plasmid pSGK005 was constructed as follows.

A 2769bp DNA segment of the monensin cluster of *S. cinnamonensis* extending from nucleotide 42438 to 45207 was amplified by PCR using the following oligonucleotide primers. 5′-GTGACGTCATATGTCGAGTGCTGAAGAGTCG-3′ and 5′-GGGGTCGCCTAGGAACCAGCGCCGCCAGTCGA-3′

The design of these primers introduced *Nde* I and *Avr* II sites at the ends of the amplifed fragment. Monensin cosmid 05 was used as a template for the reaction. The resulting 2769bp fragment was digested with *Nde* I and *Xho* I and a 656bp fragment (Fragment A) purified by preparative gel electrophoresis.

A second PCR reaction was used with the same template to amplify DNA from nucleotide 43098 to 45207. The primers used were

5′-CGGCCTCGAGGGCCCGTCGGTCAGTGTCGACACGGCGCAGTCCTCCTCGC-3′ and 5′-GGGGTCGCCTAGGAACCAGCGCCGCCAGTCGA-3′

The design of the upstream oligonucleotide primer incorporated a change of the codon specifying the KS active site cysteine (nucleotides 43135-43137, TGC) to glutamine (CAG). The resulting 2109bp DNA fragment (Fragment B) was digested with *Xho* I and *Avr* II and purified by preparative gel electrophoresis.

Plasmid pCJW80 is derived from pCJR24 and DEBS1-TE in which *Msc* I and *Avr* II sites have been introduced to flank the AT of the DEBS loading module. This plasmid was digested with *Nde* I and *Avr* II and the larger fragment (Fragment C) purified by preparative gel electrophoresis.

The three fragments (Fragments A, B, C) were ligated together using T4 DNA ligase and the ligation mixture used to transform electrocompetent *E. coli* DH10B cells. Individual clones were checked for the presence of the desired plasmid pSGK005. The identity of pSGK005 was confirmed by restriction pattern and sequence analysis.

Plasmid pSGK005 was used to transform *S. erythraea* NRRL2338 using a routine protoplast transformation technique. Thiostrepton resistant colonies were selected on R2T20 media containing g/ml thiostrepton. Further analysis confirmed that pSGK005 had integrated into the *S. erythraea* NRRL2338 chromosome by Southern blot hybridisation of their genomic DNA with DIG-labelled DNA containing the *act*II orf4 promoter. The culture *S.*

erythraea NRRL2338 (pSGK005) was inoculated into 5ml tap water medium in a 30ml flask. After three days incubation at 29°C this flask was used to inoculate 30ml of Ery-P medium in a 300ml flask. The broth was incubated at 29°C at 200rpm for 6 days. After this time the whole broth was adjusted to pH8.5 with NaOH, and then extracted twice with an equal volume of ethyl acetate. The ethyl acetate extract was evaporated to dryness at 45°C under a nitrogen stream using a Zymark Turbovap LV evaporator. The product identities were confirmed by LC/MS. A peak was observed with a m/z value of 734 $(M+H)^+$ required for erythromycin A. A second peak was observed with a m/z value of 748 $(M+H)^+$, required for 13-propyl erythromycin A.

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TABLE I

gene	function	start	end
gdhA	glutamate dehydrogenase (partial)	1038	0
dapA	dihydrodipicolinate synthase	2140	1220
orf3	putative transcriptional activator	2211	3152
orf4	hypothetical protein	3264	3680
orf5	hypothetical protein	4307	3684
orf6	hypothetical protein	4570	4758
orf7	hypothetical protein	5058	5612
acpX	acyl carrier protein	6010	5693
ksX	ketoacyl synthase	8531	6045
monCI	probable epoxihydrolase/cyclase	9542	8643
monE	methyltransferase	10426	9596
monT	monensin resistance gene (ABC-	10656	12191
monRI	probable repressor	12205	12780
monAI	thioesterase	13829	13023
monAI	polyketide synthase loading &	14121	23198
	KS-L	14172	15486
	AT-L malonate specific	15777	16880
	ACP-L	17019	17276
	KS1	17358	18626
	AT1 methylmalonate specific	18960	19976
	DH1 (potential)	20019	20519
	KR1 (inactive)	21636	22241
	ACP1	22536	22793
monAI	polyketide synthase module 2	23205	29921
	KS2	23307	24569
	AT2 methylmalonate specific	24891	25913
	DH2	25953	26369
	ER2	27600	28463
	KR2	28485	29042
	ACP2	29313	29570
monAI	polyketide synthase modules 3 & 4	29974	42372
	KS3	30076	31347
	AT3 malonate specific	31798	32838
	DH3	32884	33465
	KR3	34692	35181
	ACP3	35553	35811
	KS4	35899	37170
	AT4 methylmalonate specific	37489	38511
	DH4	38557	38982
	ER4	40123	40986
	KR4	41005	41562
	ACP4	41848	42105
monAI	polyketide synthase modules 5 & 6	42448	54564
	KS5	42628	43890
	AT5 ethylmalonate specific	44221	45243
	DH5	45289	45744
	KR5	46785	47337
	ACP5	47593	47850

	KS6	47947	49218
	AT6 malonate specific	49579	50601
	DH6	50644	51075
	ER6	52222	53102
	KR6	53101	53661
	ACP6	54052	54306
monA	polyketide synthase modules 7 & 8	54614	66934
	KS7	54716	55978
	AT7 methylmalonate specific	56300	57319
	DH7	57358	57802
	KR7	59048	59608
	ACP7	59867	60124
	KS8	60185	61453
	AT8 malonate specific	61808	62839
	DH8	62882	63316
	ER8	64577	65437
	KR8	65456	66016
	ACP8	66404	66661
monA	polyketide synthase module 9	66952	72054
	KS9	67075	68340
	AT9 malonate specific	68698	69729
	KR9 (potential)	70735	71262
	ACP9	71536	71783
monH	probable regulator	72051	74993
monCI	FAD containing epoxidase	76541	75051
monBI	double bond isomerase	76960	76538
monBI	double bond isomerase	77450	77016
monA	polyketide synthase modules 11 &	88708	77447
	KS11	88612	87344
	AT11 methylmalonate specific	87022	85993
	KR11	85111	84562
	ACP11	84292	84035
	KS12	83962	82694
	AT12 methylmalonate specific	82354	81335
	DH12 (potential) delta	81286	80855
	ER12 (potential)	79618	78914
	KR12	78895	78337
	ACP12	78070	77812
monA	polyketide synthase module 10	93741	88816
	KS10	93636	92368
	AT10 methylmalonate specific	92040	91021
	KR10	90132	89584
	ACP10	89322	89068
monD	P450 oxygenase	94081	95273
monRI	probable activator	96141	95338
monA	thioesterase	96941	96138
orf29	cell wall biosynthesis capK	97580	98953
lipB	lipase B	99983	98991
orf31	ion pump	101433	100507
orf32	membrane structural protein	102581	101490
amtA	glycine amidinotransferase	102924	103450

TABLE II

GdhA, glutamate dehydrogenase (partial coding sequence) Length: 346 amino acids

1 LTTRPDTKTA LSQKTALSQL LTEIEHRNPA QPEFHQAARE VLETLAPVIA
51 ARPEYAEAGL IERLCEPERQ IVFRVPWQDD HGRVRVNRGF RVEFNSALGP
101 YKGGLRFHPS VNLGVIKFLG FEQIFKNALT GLGIGGGKGG SDFDPRGRSD
151 AEVMRFCQSF MTELYRHIGE HTDVPAGDIG VGGREIGYLF GQYRRITNRW
201 EAGVLTGKGR NWGGSLIRPE ATGYGNVLFA AAMLRERGET LEGRTAVVSG
251 SGNVAIYTIQ KLAALGANAV TCSDSSGYVV DEKGIDLDLL KQVKEVERAR
301 VDTYAQRRGA SARFVPGRRV WEVPADIALP SATQNELDAD DATALI

DapA, dihydrodopicolinate synthase Length: 307 amino acids

1 MTLASSLEPT TEPLFNGLYV PLVTPFTDDL RLAPEALARL ADEALSAGAS
51 GLVALGTTAE AATLTAEERE TVIRVCSAAC RAHGAPLIVG VGTNDTATAI
101 TALRELAARG DVAAALVPAP PYIRPGEAGT LAHFAALAEH GGLPLVVYDI
151 PYRTGQTLGA GTITALGRLP EVVGIKHATG SIDPTTMELL DSPLPGFAVL
201 GGDDIVLSPL VAAGAHGGIV ASANLRTADY AEMIALWRRG SAAPARALGA
251 DLARLSAALF TEPNPTVIKG VLHAQNRIPS PAVRMPLLAA SADSVRRAAP
301 LAASRK*

ORF3, putative transcriptional activator protein Length: 314 amino acids

1 MLDVRRLHLL RELDRRGTIA AVAEALTFTA SAVSQQLGVL EREAGVPLLE
51 RSGRRVVLTP AGRSLVAHAD AVLNRLEQAV AELAGARDGI GGPLRIGTFP
101 SGGHTIVPGA LAELASRHPA LEPMVREIDS ARVSDGLRAG ELDVALVHDY
151 DFVPATPDTT VDEVPLLEEP MYLVTHAADT ATDSGSGSTL AALLGPCAEV
201 PWITARDGTT GHAMAVRACQ AAGFQPRIRH QVNDFRTVLA LVAAGQGAGF
251 VPRMAAEPSP AGVVLTKLPL FRRSKVAFRA GGGAHPAIAA FVAAATTAVE

301 RMAGSRGPAG GSE*

ORF4, hypothetical protein Length: 139 amino acids

1 MADDAYLFLL PDRHPRLGAA LAAVGALECT ETPAVHAWLQ AHEASVSSEQ

51 VRILPADAET LIPKDAERLP VPLSEEEALK VEQECAPQTV TDMESELLAF

101 RETTQDWQAL VHRALTAGIP AQRIARLTGL DPEEIGRL*

ORF5, hypothetical protein Length: 208 amino acids

1 LAVAACAAVV LPIDAVVRIS AADVGVLVFF AYLLPYLAIT MTVFVSVAPE

51 QVRSWARREA RGTFLQRYVL GTAPGPGGSL FIAAAALVVA VLWLPGHLST

101 TFSALPRTLV ALALVVAAWI CVVVAFAVTF QADNLVENER ALEFPGERSP

151 AWADYVYFAL AAMTTFGTTD VDVTSRDMRR TVAANTVIAF VFNTVTVAIL

201 VSALGGR*

ORF6, hypothetical protein Length: 63 amino acids

1 MTVMDKLKQM LKGHEDKAGQ GIDKAGDFVD GKTQGKYSGQ VDTAQDKLRD

51 QFGSDQQEPP QR*

ORF7, hypothetical protein Length: 185 amino acids

1 MGTAQSQEQA AAPGACAAFV RFVLCGGGVG LASSFAVVAL ASWVPWALAN

51 ALVAVVSTVV ATELHARFTF GAGGRATWRQ HAQSAGSAAA AYAVTCVAMF

101 VLQQLVAAPG AVLEQVVYLS ASALAGVARF VVLRLVVFAR NRSLPAAAAV

151 RTARPVRRVP APVPATVAHA ASRPAGPAAL CPAA*

AcpX, acyl carrier protein (ACP) Length: 106 amino acids

1 MTSTDHTSGQ DATELEKQLA AATPEEREKL LTDTIRTQAG TLLNTTLSDD

51 SNFLENGLNS LTALELTKTL MTLTGMEIAM VAIVENPTPA QLAHHLGQEL

101 AHTTA*

KsX, ketoacyl-ACP synthase Length: 829 amino acids

1 VANEEKLVEY LKWTTAELHQ AQQQLRELKA AQHEPIAVVS MACRLPGKTR
51 TPDDLWDLVS EGRDAVTGFP DDRAWELPEE RPYAELGGFL DDAAGFDAGF
101 FDISDTEAVA TEPLQRLMLH LAWETVERGH IAPHTLRSTL TGVYVGATGH
151 DYATRLETAP DELLPYLGGG TSGSLVSGRI AYALGLEGPA ISVDTACSSS
201 LVALHLACQA LRRGECGLAL AGGGTVMSTP HTFHAFAHQK SLAQDGRCKP
251 FAAAADGMGL GEGVGLVLLE RLGDARKNGH PVLAVIRGSA VNQDGAGYGL
301 AAPNGPSQQH VIRAALADAG LTPDQIDAVE AHGTGTPIGD AIEVQALLAT
351 YGADRSPDRP LWLGSVKSNT GHTQGAAGAA ALIKMVQAFR HGTLPPTLHV
401 DRPTPLAAWK KGAVRLLTEA VDWPRREEPR RVGISAFATS GTNAHLILEE
451 PPVDEAPVPD AARDQTSPVA PELPVAWSLS ARTPEALRAQ AKALVTHLAA
501 TDPAPSPAEV AYSLAATRSP LEHRAVLTGT DHTELLAAAR ALAAGEDHPD
551 LVRSTPGAGP KKIAWHFDGR PADGVTTGAA PGAKPGATFG ATFGAAFGGA
601 EFHSAFPLFA SAFDEARALL DTHLPTPLPT PHSELARFAV HTALARLLLE
651 TGVRPHTLTG DGVGHIAAAY AAGILTLDDA CRLAAAHAAA AQAAEGEQPA
701 PPDAYEPVLK QLTFQRATLT LTSTAPADTP IASADYWHHH LTSPAPTAPP
751 TPETHTLLHL GALSPEGTQT SAVSALLTAL ARLHTTGGTV DWTPLVRRTP
801 HPRTIDLPTY SFQATRYWLH DHTAHAAV*

MonCII, probable epoxyhydrolase/cyclase Length: 300 amino acids

1 VKNLRIPVSQ TVSLNVRYRP ADGPGAPGRP FLLLHGMLSN ARMWDEVAAR
51 LAAAGHPAYA VDHRGHGESD TPPDGYDNAT VVTDLVAAVT ALDLSGALVA
101 GHSWGAHLAL RLAAEHPDLV AGLALIDGGW YEFDGPVMRA FWERTADVVR
151 RAQQGTTSAA DMRAYLRATH PDWSPTSIEA RLADYRVGPD GLLIPRLTST
201 QVMSIVAGLQ REAPADWYPK VTVPVRLLPL IPAIPQLSDQ VRAWVAAAEA

251 ALEQVSVRWY PGSDHDLHAG APDEIAADLL LLARSCEAMP GGKAGVRPA*

MonE, S-adeonosylmethionine-dependent methyltransferase Length: 277 amino acids

1 VNKTVAPEPS DIGHYYDHKV FDLMTQLGDG NLHYGYWFDG GEQQATFDEA
51 MVQMTDEMIR RLDPAPGDRV LDIGCGNGTP AMQLARARDV EVVGISVSAR
101 QVERGNRRAR EAGLADRVRF EQVDAMNLPF DDGSFDHCWA LESMLHMPDK
151 QQVLTEAHRV VKPGARMPIA DMVYLNPDPS RPRTATVSDT TIYAALTDIG
201 DYPDIFRAAG WTVLELTDIT RETAKTYDGY VEWIRAHRDE YVDIIGVEGY
251 ELFLHNQAAL GKMPELGYIF ATAQRP*

MonT, putative monensin resistance gene (ABC-transporter) Length: 512 amino acids

1 MSADLGARRW WAVGALVLAS MVVGFDVTIL SLALPAMADD LGANNVELQW
51 FVTSYTLVFA AGMIPAGMLG DRFGRKKVLL TALVIFGIAS LACAYATSSG
101 TFIGARAVLG LGAALIMPTT LSLLPVMFSD EERPKAIGAV AGAAMLAYPL
151 GPILGGYLLN HFWWGSVFLI NVPVVILAFL AVSAWLPESK AKEAKPFDIG
201 GLVFSSVGLA ALTYGVIQGG EKGWTDVTTL VPCIGGLLAL VLFVMWEKRV
251 ADPLVDLSLF RSARFTSGTM LGTVINFTMF GVLFTMPQYY QAVLGTDAMG
301 SGFRLLPMVG GLLVGVTVAN KVAKALGPKT AVGIGFALLA AALFYGATTD
351 VSSGTGLAAA WTAAYGLGLG IALPTAMDAA LGALSEDSAG VGSGVNQSIR
401 TLGGSFGAAI LGSILNSGYR GKLDLDGVPE QAHGAVKDSV FGGLAVARAI
451 KSNGLADSVR SAYVHALDVV LVVSGGLGLL GVVLAVVWLP RHVGQSTAKT
501 AESEHEAADA V*

MonRII, probable repressor protein Length: 192 amino acids

1 VPGLRERKKA RTKAAIQREA VRLFREQGYT ATTIEQIAEA AEVAPSTVFR
51 YFATKQDLVF SHDYDLPFAM MVQAQSPDLT PIQAERQAIR SMLQDISEQE

101 LALQRERFVL ILSEPELWGA SLGNIGQTMQ IMSEQVAKRA GRDPRDPAVR

151 AYTGAVFGVM LQVSMDWAND PDMDFATTLD EALHYLEDLR P*

MonAIX, thioesterase Length: 269 amino acids

1 MDRGTAARAP QIGDEFGAAT GNGVWLRRYH AAAEAPVRLV CFPFAGGSAS

51 YYFGLSGLLA PGVEVLAVQY PGRQDRHAEP CLASVAELAD GVVPHLPCDG

101 KPFALFGHSL GAIVAFEVAR RLRGPAGPGL PVHLFVSGGL ARPYRPAGRS

151 GAFGDADILA HLRAMGGTDE RFFRSPELQE LVLPALRADY RAVATYEAPG

201 PGRLDCPITA LIGDADERTS PEQAATWRER TGAAFDLRVL PGGHFYLDGC

251 QEQVAAVVTE ALTAGPGV*

MonAI, polyketide synthase multi-enzyme MONS1, housing loading module and extension module 1 Length: 3026 amino acids

1 MAASASASPS GPSAGPDPIA VVGMACRLPG APDPDAFWRL LSEGRSAVST

51 APPERRRADS GLHGPGGYLD RIDGFDADFF HISPREAVAM DPQQRLLLEL

101 SWEALEDAGI RPPTLARSRT GVFVGAFWDD YTDVLNLRAP GAVTRHTMTG

151 VHRSILANRI SYAYHLAGPS LTVDTAQSSS LVAVHLACES IRSGDSDIAF

201 AGGVNLICSP RTTELAAARF GGLSAAGRCH TFDARADGFV RGEGGGLVVL

251 KPLAAARRDG DTVYCVIRGS AVNSDGTTDG ITLPSGQAQQ DVVRLACRRA

301 RITPDQVQYV ELHGTGTPVG DPIEAAALGA ALGQDAARAV PLAVGSAKTN

351 VGHLEAAAGI VGLLKTALSI HHRRLAPSLN FTTPNPAIPL ADLGLTVQQD

401 LADWPRPEQP LIAGVSSFGM GGTNGHVVVA AAPDSVAVPE PVGVPERVEV

451 PEPVVVSEPV VVPTPWPVSA HSASALRAQA GRLRTHLAAH RPTPDAARVG

501 HALATTRAPL AHRAVLLGGD TAELLGSLDA LAEGAETASI VRGEAYTEGR

551 TAFLFSGQGA QRLGMGRELY AVFPVFADAL DEAFAALDVH LDRPLREIVL

601 GETDSGGNVS GENVIGEGAD HQALLDQTAY TQPALFAIET SLYRLAASFG

651 LKPDYVLGHS VGEIAAAHVA GVLSLPDASA LVATRGRLMQ AVRAPGAMAA

701 WQATADEAAE QLAGHERHVT VAAVNGPDSV VVSGDRATVD ELTAAWRGRG

751 RKAHHLKVSH AFHSPHMDPI LDELRAVAAG LTFHEPVIPV VSNVTGELVT

801 ATATGSGAGQ ADPEYWARHA REPVRFLSGV RGLCERGVTT FVELGPDAPL

851 SAMARDCFPA PADRSRPRPA AIATCRRGRD EVATFLRSLA QAYVRGADVD

901 FTRAYGATAT RRFPLPTYPF QRERHWPAAA GVGQQPETPE LPESSESSEQ

951 AGHEREEGAR AWGGPEGRLA GLSVNDQERV LLGLVTKHVA VVLGDASGTV

1001 QAARTFKQLG FDSMAAAELS ERLGTETGLP LPATLTFDYP TPLAVAAHLR

1051 AELTGTPAPA GSAPATGALG AGDLGTDEDP VAIVAMSCRY PGGAGTPEDL

1101 WRLVADGADA IGDFPTDRGW DLARLFHPDP DRSGTSCTRQ GGFLYDAADF

1151 DAEFFDISPR EALAVDPQQR LLLECAWEAF ERAGLDPRAL KGSPTGVFVG

1201 MTGQDYGPRL HEPSQATDGY LLTGSTPSVA SGRLSFSFGL EGPALTVDTA

1251 CSSSLVTLHL AAQALRRGEC DLALAGGATV LATPGMFTEF SRQRGLAPDG

1301 RCKPFAAGAD GTGWAEGVGL VLLERLSEAR RKGHAVLAVI RGSAINQDGA

1351 SNGLTAPNGP SQQRVIRAAL AAARLTADEV DVVEAHGTGT TLGDPIEAQA

1401 LLATYGQGRS AERPLWLGSV KSNIGHTQAA AGVAGVIKMV MAMRHDLLPA

1451 TLHVDEPSGH VDWSTGAVRL LTEPVVWPRG ERPRRAAVSS FGISGTNAHL

1501 VLEEAGQDEY VAGAADDAGP VDGAVLPWVV SGRTGAALRE QARRLRELVT

1551 GGSADVSVSG VGRSLVTTRA VFEHRAVVVG RDRDTLIGGL EALAAGDASP

1601 DVVCGVAGDV GPGPVLVFPG QGSQWVGMGA QLLGESAVFA ARIDACEQAL

1651 SPYVDWSLTE VLRGDGRELS RVDVVQPVLW AVMVSLAAVW ADHGVTPAAV

1701 VGHSQGEIAA VVVAGALTLE DGAKIVALRS RALRQLSGGG AMASLGVGQE

1751 QAAELVEGHP GVGIAAVNGP SSTVISGPPE QVAAVVADAE ARELRGRVID

1801 VDYASHSPQV DAITDELTHT LSGVRPTTAP VAFYSAVTGT RIDTAGLDTD

1851 YWVTNLRRPV RFADAVTALL ADGHRVFIEA SSHPVLTLGL QETFEEAGVD
1901 AVTVPTLRRE DGGRARLARS LAQAFGAGCA VRWENWFPAT GTSTVELPTY
1951 AFQRRRYWLE APTGTQDAAG LGLAAAGHPL LGAATEIADG DIRLLTGRIS
2001 RHSHPWLAQH TLFGAAVVPA SVLAEWALRA ADEAGCPRVD DLTLRTPLVL
2051 PETAGVQVQI VVGPADARDG HRDFHVYARP DGKDASEGEG IAEGEGASEG
2101 EGASGGTDAP WTCHADGRLV AEPTGTASED SPDTVWPPPG AEPVDLGDFY
2151 ERAAATGVGY GPVFTGLRAL WRRDGELFAE AVLPQEAPET AGFGMHPALL
2201 DAALHPALLG ERPAEEDKVW LPFTLTGVTL WATGATSVRV RLTPLDDDPD
2251 ASADGRAWRV GVSDPTGAEV LTCEALVAVA AGRRELRAAG ERVSDLYAVE
2301 WVPVPGPGPV GEGADFSGWA GLGECGERWE CVGRVERWYE DLDALGAAVE
2351 GGASVPSVVL ATAAAAPGGA GDGAADALSA VRWTGALLDQ WLADARFADA
2401 RLVVITSGAV ATGDDFLPDP AAAAVRGLVE QAQVRHPGRI LLVDTEAGAG
2451 LGVGAGVDDA LLEQAVAMAL GADEPQLALR AGRVLAPRLT APQDAAVTEA
2501 ARPLDPDGTV LITGPAGAPV ADLAEHLVRT GQCRHLLLLP GDGELEEMAE
2551 ELRGLGATVD LSTADPADPT ALAEVVAAVE GDHPLTGVIH ATGVVDAFDP
2601 GDSASDLMID SASDSFAEAW SSRAGVTAAL HTATAHLPLD LFAVLSPAGA
2651 DLGIARSAAA AGADAFSAAL ALRRHTTVTT DTTAPPRTTA PPRTTASPRT
2701 TALSSSRTTG VALAYGPPTA PRPGIKGTAP GRIPVLLDAA RAHGGGSPLL
2751 GARLAARALA AESAAEGVAG LPAPLRALAV AAAAAGAPTR RTAADRKPPA
2801 DWPARLAPLS APEQLRLLID AVRTHAAAVL GRTDPEALRG DATFKQLGLD
2851 SLTAVELRNR LVEDTGLRLP TALVFRYPTP AAIAAHLRER LTSPSETTAT
2901 QRSGGQTPAA GQASSALAPG GSAAGPPAAD TVLSDLTRME NTLSVLAAQL
2951 PHTETGEITT RLEALLTRWK TTNATANDSG DGNGGDDDAA ERLKAASADQ
3001 IFDFIDNELG VGHGTSRVTP TPKAG*

SUBSTITUTE SHEET (RULE 26)

MonAII, polyketide synthase multi-enzyme MONS2, housing extension module 2 Length: 2239 amino acids

1 MASEEQLVEY LRRVTTELHD TRRRLVQEED RRQEPVALVG MACRFPGGVA

51 SPEDLWDLVA AGKDAIEDFP TDRGWDLEAL YDPDPAAYGT SYVRHGGFVD

101 DAGSFDADFF GISPREALAM DPQQRLMLET SWELFERAGI EPVSLKGSRT

151 GVYAGVSSED YMSQLPRIPE GFEGHATTGS LTSVISGRVA YNYGLEGPAV

201 TVDTACSASL VAIHLASQAL RQRECDLALA GGVLVLSSPL MFTEFCRQRG

251 LAPDGRCKPF AAAADGTGFS EGIGLLLLER LSDARRNGHK VLAVIRGSAV

301 NQDGASNGLT APNDAAQEQV IRAALDNARL TPSEVDAVEA HGTGTKLGDP

351 IEAGALLATY GQHRARPLLL GSLKSNIGHT HATAGVAGVI KTVMAIRNGL

401 LPATLHVEEL SPHVDWDAGA VEVVTEPTPW PETGHPRRAG VSAFGISGTN

451 AHLILEEAPP EEDVPAPVVV ESGGVVPWVV SGRTPEALRE QARRLGEFVA

501 GDTDALPNEV GWSLATTRSV FEHRAVVVGR DRDALTAGLG ALAAGEASAG

551 VVAGVAGDVG PGPVLVFPGQ GAQWVGMGAQ LLDESAVFAA RIAECERALS

601 AHVDWSLSAV LRGDGSELSR VEVVQPVLWA VMVSLAAVWA DYGVTPAAVI

651 GHSQGEMAAA CVAGALSLED AARIVAVRSD ALRQLQGHGD MASLSTGAEQ

701 AAELIGDRPG VVVAAVNGPS STVISGPPEH VAAVVADAEA RGLRARVIDV

751 GYASHGPQID QLHDLLTERL ADIRPTNTDV AFYSTVTAER LTDTTALDTD

801 YWVTNLRQPV RFADTIEALL ADGYRLFIEA SAHPVLGLGM EETIEQADMP

851 ATVVPTLRRD HGDTTQLTRA AAHAFTAGAD VDWRRWFPAD PAPRTIDLPT

901 YAFQRRRYWL ADTVKRDSGW DPAGSGHAQL PTAVALADGG VVLNGRVSAE

951 RGGWLGGHVV AGTVLVPGAA LVEWVLRAGD EAGCPSLEEL TLQAPLVLPE

1001 SGGLQVQVVV GAADEQGGRR DVHVYSRSEQ DASAVWQCHA VGELGRASVA

1051 RPVRQAGQWP PAGAEPVEVG GFYEGVAAAG YEYGPAFRGL RAMWRHGDDL

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1101 LAEVELPEEA GSPAGFGIHP ALLDAALHPL LAQRSRDGAG AGAHGGQVLL

1151 PFSWSGVSLW ASEATTVRVR LTGLGGGDDE TVSLTVTDPA GGPVVDVAEL

1201 RLRSTSARQV RGSAGPGADG LYELRWTPLP EPLPVPAPAN GRDVAADLSG

1251 CAVLGELVAE PGPGIDLEGC PCYPGVGALA DNASPPSMIL APVHSDTTGG

1301 DGLALTERVL RVIQDFLAAP SLEQKQTRLA FVTRGAADTG STTGGSAAPA

1351 EAVDPAVAAV WGLVRSAQSE NPGRFVLLDT DAPLDQASVA PLVDAVRSAV

1401 EADEPQVALR GGRLLVPRWA RAGEPVELAG PAGARAWRLV GGDSGTLEAV

1451 VAEACDDIVL RPLAPGQVRV AVHTAGVNFR DVLIALGMYP DPDALPGTEA

1501 AGVVTEVGPG VTRLSVGDRV MGMMDGAFGP WAVADARMLA PVPPGWGTRQ

1551 AAAAPAAFLT AWYGLVELAG LKAGERVLIH AATGGVGMAA VQIARHVGAE

1601 VFATASPGKH AVLEEMGIDA AHRASSRDLA FEDAFRQATD GRGVDVVLNS

1651 LTGELLDASL RLLGDGGRFV EMGKSDPRDP ELVALEHPGV SYEAFDLVAD

1701 AGPERLGLML DRLGELFAGG SLVPLPVTAW PLGRAREALR HMSQARHTGK

1751 LVLDVPAPLD PDGTVLVTGG TGTIGAAVAE HLARTGESKH LLIVSRSGPA

1801 AHGAEELVSR IAEFGAEATF VAADVSEPDA VAALIEGIDP AHPLTGVVHA

1851 AGVLDNALIG SQTTESLTRV WAAKAAAAQQ LHEATRESRL GLFVMFSSFA

1901 STMGTPGQAN YSAANAYCDA LAALRRAEGL AGLSVAWGLW EATSGLTGTL

1951 SAADRARIDR YGIRPTSAAR GCALLAAARA HGRPDLLAMD LDARVPAASD

2001 APVPAVLRTL AAAGAPATAR PTAAAAADGA TDWSGRLAGL TEEARLELLT

2051 ELVCTHAAGV LGHADAGAVQ VDAPFKELGF DSLTAVELRN RIAAATGLKL

2101 PAALVFDYPQ ARVLAAHLAE RLVPEGAGAM GGVSGAEGVR DAYGAGGPGG

2151 DMTAQVLLEV ARVEHTLSAA VPHGLDRAAV AARLEALLAR CTATTAATGA

2201 AGAAVEGDGD SDGDGAVDQL ETATAEQVLD FIDNELGV*

MonAIII, polyketide synthase multi-enzyme MONS3, housing extension modules 3 and 4 Length: 4133 amino acids

1. MVSEEKLVDY LKRVSADLHA TRQRLREAEE RGQEPVAVVE AACRYPGGIR

51 TPEDLWDLVA AGGNALGAFP DNRGWDLRRL FHPDPDHPGT TYAREGGFLH

101 DADLFDPEFF GISPREAAVL DPQQRLLLEC AWEALERAGI DPRSLQGSRT

151 GVYAGAALPG FGTPHIDPAA EGHLVTGSAP SVLSGRLAYT FGLEGPAVTI

201 DTACSSSLVA VHLAAHALRQ RECDLALAGG VTVMTTPYVF TEFSRQRGLA

251 ADGRCKPFAA AADGTAFSEG AGLLVLERLS DARRAGHRVL AVIRGSAVNQ

301 DGASNGLTAP NGPAQQRVIR AALAGARLSP AEVDAVEAHG TGTRLGDPIE

351 ADALLATYGQ ERHGGRPLWL GSVKSNIGHT QGAAGAAGLI KMVQALRHET

401 LPATLYADEP TPHADWESGA VRLLSAPVAW PRGEHGEHTR RAGISSFGIS

451 GTNAHLILEE APAADAEGAG GDGDGDGGGV RPVVRVGATG PREEQGQGQG

501 QEQHQQQRQQ RQRSSMMPTP HLPWLLSARS PAALRAQADA LANHVAHADH

551 SIADIGGTLL RRTLFEHRAV VLGTDRDERA AALAALAAGR AHPALTRAAG

601 PARNGGTAFL FTGQGSQRPG MGRQLYDTFD VFAESLDETC ARLDPLLEQP

651 LKPVLFAPAD TAQAAVLHGT GMTQAALFAL EVALYRQVTS FGIAPSHLTG

701 HSVGEIAAAH VAGVFSLADA CTLVAARGRL MQALPAGGAM LAVQAAEDDV

751 LPLLAGQEER LSLAAVNGPT AVVVSGEAAA VGEVEKALRG RGLKTKRLNV

801 SHAFHSPLIE PMLDDFREVA RGLTFHAPTL PVVSNLTGRL ADAELMADAE

851 YWVRHVRRPV RFHDGLRALS EQGVVRYLEL GPDPVLATMV QDGLPAPAEG

901 EEPEPVVAAA LRSKHDEGRT LLGAVAALHT DGQPADLTAL FPADAGQVPL

951 PTYRFQRRRY WRVAPDAAAP ARAAGLQETG HPLLPAVIRQ ADGGILLAGR

1001 LSLRTHPWLA DHTIAGGVPL PATAFVELAL LAGRHAACDT IDDLTLETPL

1051 LLDDTGTGVG AAVGAGADAL VDAIEVQLAL GAPDGSGRRA LTVHSRPADD

1101 AADDGDAADA ADAAGRGGPG GSGDLGDPGD PGDLGDGGGS RGWRRHATGI

1151 LSAGPAAEPA APDAAPWPPA DATALDVDAL YARLDAQGYS YGPAFRAVHA

1201 AWRHGDDLYA DVRLADEQRA EADAFALHPA LLDAALHAVD ELYRGSEGRG

1251 QEQGQGGQEP EQGRGDADAP VRLPFSFSDI RHHATGATRL WVRLSPQGDD

1301 RLRLSLTDGE GGQVATVDAL QLRLIPADRW RAARPTTAAP LYHLDWHELP

1351 LPEPAETDPA AHSWAVLGAH DAGLAPAAHY PDLAALKAAV EAGEPVPDIV

1401 FAPFPAQGTE TDVPAQVRAH ARHALELLRD WLTTEAFAAA RLVVLTTGAV

1451 TARPEDGPAD LATAPVWGLV RAAQAEQPDH VVLVDIDKDI DKDTDEETDQ

1501 ATDAGTASRH ALPAALAAAA AQAETQLALR AGTVLVPRLA VVPPRTDTPA

1551 LHATAPESTT DTVDSTGIAG AAESGGTVLI TGGTGGLGQA VARHLAAAHG

1601 ARHLLLVSRR GDAAEGVAEL RADLADDGVD VRVAACDITD RDALAGLLAD

1651 IPAAHPLTAV VHTAGVIDDS LITAMTPERL DAVLAPKADA AWHLHELTRD

1701 KDLSAFVLFS SGASVLGNGG QANYAAANTF LNTLAEHRRA AGLAATSVAW

1751 GLWESASGGM AARLGDADRA RIHRTGVTGL TDEQALALFD AALTAEHPTV

1801 LATRFDRAVL RGQAAARTLQ PALRGLVRTP RPTASAGAIG STAATGSATD

1851 ENAPSSWAAR LARLSAADRD RALNELIREQ IATVLAHPSP DTIELGRAFQ

1901 ELGFDSLTAL ELRNRLSTAT GIRLPATLVF DHPSPTALVR HLHSHLPDEA

1951 QHTSPTAPGA SAEGTAATAT GIDDDPIAIV GMACRYPGGV TSPEQLWQLV

2001 ATGTDAIGPF PEDRGWDTAG LFDPDPDQVG HSYTREGGFL YDAARFDAGF

2051 FGISPREAAA TDPQQRLLLE TAWQAFEHAG IDPAALRGTP CGVITGIMYD

2101 DYGSRFLARK PDGFEGRIMT GSTPSVASGR VAYTFGLEGP AITVDTACSS

2151 SLVAMHLAAQ ALRQGECELA LAGGVTVMAT PNTFVEFSRQ RGLAPDGRCK

2201 PFAAAADGTG WGEGAGLVVL ERLSDARRKG HRVLALLRGS AVNQDGASNG

2251 MTAPNGPSQE RVIRTALAGA GRGPEDIDVV EAHGTGTTLG DPIEAQALLA

2301 TYGQGRPEDR PLWLGSVKSN IGHTQAAAGV AGVIKMVMAL RHEQLPTTLH

2351 ADEPTPHVQW DGGGVRLLTE PVPWSRGERT RRAGVSSFGI SGTNAHLILE
2401 EPPEEDLPEP VAAEPGGVVP WVVSGRTPDA LREQARRLGE FVVGAGDVSA
2451 AEVGWSLATT RSVFEHRAVV AGRDRDDLVA GMQALAAGET PTDVVSGAAA
2501 SSGAGPVLVF PGQGSQWVGM GAQLLDESPV FAARIAECEQ ALSAYVDWSL
2551 SDVLRGDGSE LSRVEVVQPV LWAVMVSLAA VWADYGVTPA AVVGHSQGEM
2601 AAACVAGALS LEDAARIVAV RSDALRQLQG HGDMASLGTG AEQAAELIGD
2651 RPGVVVAAVN GPSSTVISGP PEHVAAVVAE AEARGLRARV IDVGYASHGP
2701 QIDQLHDLLT EGLADIRPAN TDVAFYSTVT AERLTDTTAL DTDYWVTNLR
2751 QPVRFADTIE ALLADGYRLF IEASAHPVLG LGMEETIEQA DIPATVVPTL
2801 RRDHGDTTQL TRAAAHAFTA GADVDWRRWF PADPTPRTVD LPTYAFQHQH
2851 YWLEEPSGLT GDAADLGMVA AGHPLLGACV ELAESDSYLF TGRLSRRAPS
2901 WLAEHVVAGT VLVPGAALVE WVLRAGDEAG CPTIEELTLQ APLVLPESGG
2951 LQVQVVVGAT DEQSGRRDVH VYSRSEQDAS AVWVCHAVGV VSSEMPEAAA
3001 ELSGQWPPAG AEAVDVEDFY ARAAEAGYAY GPAFQGLRAL WRHGTELFAE
3051 VVLPEQAGGH DGFGIHPALL DAALHPLMLL DRPADGQMWL PFAWSGVSLN
3101 ADRATHVRVR LSPRGEAAER DLRVVIADAT GAPVLTVDAL TLRAADPGRL
3151 GAAARGGVDG LYTVDWTPLP LPQPLPLPRT DAGGSADWVI LSDNSSAALA
3201 DAVSSATAAG GGAPWALLAP VGGGSADDGL PVVRRTLSLV QEFLAAPELT
3251 ESRLVIVTRG AVATDADGDV AASAAAVWGL IRSAQSENPG RFVLLDVEEE
3301 HLHPDGGELP YAALRHAVEE LDEPQLALRS GKFLVPRMTP AAAPEELVPP
3351 VGTSGWRLGT SGTATLENLS VIDAPEAFAP LEPGQVRISV RAAGMNFRDV
3401 LIALGMYPDK GTFAGSEGAG HVTEVGPGVT HLSVGDRVMG LFEGAFAPLA
3451 VADARMVVPI PEGWSFQEAA AVPVVFLTAW YGLVDLGRLR AGESLLIHAG
3501 TGGVGMAATQ IARHLGAEVF ATASPAKHGV LDGMGIDAAH RASSRDLDFE

3551 ETLRAATGGR GMDVVLNSLA GEFTDASLRL LAEGGRMVDM GKTDKRDPDR
3601 VAAEHAGAWY RAFDLVPHAG PDRIGEMLAE LGELFASGAL APLPVQTWPL
3651 GRAREAFRFM SQAKHTGKLV LEIPPALDPD GTVLITGGTG VLAAAVAEHL
3701 VREWGVRHLL LAGRRGSEAP GSSELAEELT ELGAEVTFAA ADVSDPDAVA
3751 ELVGKTDPAH PLTGVIHAAG VLDDAVVTAQ TPESLARVWA AKATAAHLLH
3801 EATREARLGL FLVFSSAAAT LGSPGQANYA AANAYCDALV RQRRAEGLAG
3851 LSIGWGLWQT ASGMTGHLGE TDLARMKRTG FTPLTTEGGL ALLDAARAHG
3901 RPHVVAVDLD ARAVAAQPAP SRPALLRALA AGATPGARTA RRTAAAGSVA
3951 PAGGLADRLA GLPHPERRRL LLDLVRGNVA GVLGHSDHDA VRPDTSFKEL
4001 GFDSLTAVEL RNRLAAATGL KLPAALVFDY PESATLVDHL LERLSPDGAP
4051 PPVKDAADPV LNDLGRIESS LDALALDADA RSRVTRRLNT LLSKLNGAAT
4101 AGSPADVTDL DALDALDDVS DDEMFEFIDR EL*

MonAIV, polyketide synthase multi-enzyme MONS4, housing extension modules 5 and 6 Length: 4039 amino acids

1 MSSAEESSPD VSGTGVSGTG ESATGTSSTE AKLRQYLKRV TVDLGQARRR
51 LREVEERAQE PIAIVSMACR FPGDTRTPEA LWDLVAEGGD AIDDFPTNRG
101 WDLESLYHPD PDHPGTSYVR RGGFLYDAPA FDASFFGISP REALAMDPQQ
151 RVLMETAWQL LERAGIDPAS LKLSATGVYI GAGVLGFGGA QPDKTVEGHL
201 LTGSALSVLS GRISFTLGLE GPSVSVDTAC SSSLVSMHLA AQALRQGECD
251 LALAGGVTVM STPGAFTEFS RQGALSPDGR SKAFAASADG TGFSEGAGLL
301 LLERLSDARR NGHKVLAVIR GSAVNQDGAS NGLTAPNGPS QERVIRAALA
351 NAGLGAAEVD AVEAHGTGTK LGDPIEAGAL LATYGRDRDE DRPLWLGSVK
401 SNIGHPQGAA GVAGVIKMVM ALQRELLPAT LYVDEPTPHV DWSSGSVRLL
451 TEPVPWTRGE RPRRAGVSAF GMSGTNAHVI LEEAPPEEAA AAETPAEGTG
501 AVVPWVVSGR GEEALRAQAA QLAEHVRDDD QRPASPLEVG WSLATTRSVF

551 ENRAVVVGDD RDALLDGLRS LAAGEASPDV VSGAVGPTGP GPVMVFPGQG
601 GQWVGMGARL LDESPVFAAR IAECEQALSA YVDWSLTDVL RGDGSELARI
651 DVVQPVLWAV MVALAAVWAD QGIEPAAVVG HSQGEIAAAC VVGAISLDEA
701 ARIVAVRSVL LRQLSGRGGM ASLGMGQEQA ADLIDGHPGV VVAAVNGPSS
751 TVISGPPEGI AAVVADAQER GLRARAVASD VAGHGPQLDA ILDQLTEGLA
801 GIRPAATDVA FYSTVTAGHL TDTTELDTAY WVRNVRRTVR FADTIDALLA
851 DGYRLFIEVS PHPVLNLALE GLIERAAVPA TVVPTLRRDH GDTTQLARAA
901 AHAFAAGADV DWRRWFPADP APRTVDLPTY AFQRQDFWPA PAGGRSGDPA
951 GLGLAASGHP LLGASVGLAS GDVHLLSGRV SRQSAAWLDD HVVAGQALVP
1001 GAAQVEWVLR AGDDAGCSAL EELTLQTPLV LPDTGGLRIQ VVVEAADAHG
1051 RRDVRLFSRP DDDDAFASTH PWTCHATGVL APAPTDGTNG TRDAADTLDG
1101 AWPPADAEPV PADDLYAQAD RTGYGYGPAF RGVRALWRHG KDVLAEVTLP
1151 KEAGDPDGFG IHPALLDAVL QPAALLLPPT DAEQVWLPFA WNDVALHAVR
1201 ATTVRVRLTP LGERIDQGLR ITVADAVGAP VLTVRDLRSR PTDTGRLAAA
1251 ATRDRHGLFD LEWIAPENAA ENAAGPARDA SEGWVTLGED AASLADLLAS
1301 VEAGAPAPQL VAAPVEPDRT DDGLALATHV LDLVQTWLAS PLHDSRLVLV
1351 TRGAVTDADV DVAAAAVWGL VRSAQSEHPG RFTLIDLGPD DTLAAAMQAA
1401 HLEEPQLAVH GGEIRVPRLV RATTDPTAPN GTPEADRTAD PSEGLHRNGT
1451 VLITGGTGVL GRLVAEHLVT EWGVRHLLLA SRRGDQAPGS AELRARLSEL
1501 GASVEIAPAD VGDAEAVAAL IASVDPAHPL TGVIHAAGVL DDAVITAQTP
1551 ESLARVWATK ATAARHLHEA TRETPLDFFV VFSSAAASLG SPGQANYAAA
1601 NAYCDALVQH RRAQGLAGLS IAWGLWQATS GMTGQLSETD LARMKRTGFA
1651 ALTDEGGLAL LDAARAHDRA YVVAADLDPR AVTDGLSPLL RALTAPATRR
1701 RVASEGLADG ALATRLAGLD ADGRLRLLTD VVREYVAAVL GHGSAARVGV

1751 DIAFKDLGFD SLTAVELRNR LSAACDVRLP ATLIFDHPTP QALATHLVDR
1801 LAGSTSATTT VNATAPAAAH VAAGADVDAD TDDPVAIVAM TCRFPGGVAS
1851 PDDLWDLLDA RKDAMGAFPT DRGWDLERLF HPDPDHPGTS YTDQGGFLPD
1901 AGDFDAAFFG INPREALAMD PQQRLLLEAS WEVLERAGID PTTLKGTPTG
1951 TYVGLMYHDY AKSFPTADAQ LEGYSYLAST GSMVSGRVAY TLGLEGPAVT
2001 VDTACSSSLV SIHLATQALR HGECDLALAG GVTVMADPDM FAGFSRQRGL
2051 SPDGRCKAYA AAADGVGFSE GVGVLLLERL SDARRHGRRV LGVVRGSAVN
2101 QDGASNGLTA PNGPSQERVI RQALASGGLS SVDVDVVEGH GTGTTLGDPI
2151 EAQALLATYG QGRPEDRPLW LGSVKSNIGH TQAAAGVAGV IKMVMAMRHG
2201 VVPASLHVDV PSPHVEWDSG AVRLAVESVP WPQVEGRPRR AGVSSFGASG
2251 TNAHVIVESV PDGLEEDSVS VGGEALETET DGRLVPWVVS ARSPQALRDQ
2301 ALRLRDFASD ASFRAPLADV GWSLLKTRAL HEHRAVVVGA ERAELIAALE
2351 ALATGEPHAA LVGPACSQAR VGGDDVVWLF SGQGSQLVGM GAGLYERFPV
2401 FAAAFDEVCG LLEGPLGVEA GGLREVVFRG PRERLDHTVW AQAGLFALQV
2451 GLARLWESVG VRPDVVLGHS IGEIAAAHVA GVFDLADACR VVGARARLMG
2501 GLPEGGAMCA VQATPAELAA DVDGSAVSVA AVNTPDSTVI SGPSDEVDRI
2551 AGVWRERGRK TKALSVSHAF HSALMEPMLA EFTEAIRGVK FRQPSIPLMS
2601 NVSGERAGEE ITDPEYWARH VRNAVLFQPA IAQVADSAGV FVELGPAPVL
2651 TTAAQHTLDE SDSQESVLVA SLAGERPEES AFVEAMARLH TAGVAVDWSV
2701 LFAGDRVPGL VELPTYAFQR ERFWLSGRSG GGDAATLGLV AAGHPLLGAA
2751 VEFADRGGCL LTGRLSRSGV SWLADHVVAG AVLVPGAALV EWALRAGDEV
2801 GCVTVEELML QAPLVVPEAS GLRVQVVVEE AGEDGRRGVQ IYSRPDADAV
2851 GGDDSWICHA TGVLSPESAR LDTELGGVWP PAGAEPLDVD GFYAQAGEAG
2901 YGYGPAFRGL RAVWRHGQDL LAEVVLPEAA GAHDGYGIHP ALLDATLHPL

2951 LAARFMDGSE DDQLYVPFGW AGVSLRAVGA TTVRVRLRPV GESVDQGLSV
3001 TVTDATGGPV LSVDSLQTRP VKPSQLAAAQ QPDVRGLFTV EWTPLPQTDA
3051 DGEADWVVLS DGVGRLADVV SAAGGEAPWA VVAPVDASVG DGREGLDGRL
3101 VVERVLSLVQ EFLALPELAE SRLLVVTRGA VATGVDGDGD VDASAAAVWG
3151 LVRSAQSENP GRFILLDVDG DGDDQGPDLN GRHLPHATLR HAAEELDEPQ
3201 LALREGTLYV PRLTQARQSA ELVVPPGEPA WRLRMVHDGS LDALAAVACP
3251 EALEPLAPGQ VRIAVHAAGI NFRDVLVALG MVPAYGAMGG EGAGVVTEVG
3301 PEVTHVSVGD RVMGVFEGAF GPVVIAEARM VTPVPQGWDM REAAGIPAAF
3351 LTAWYGLVEL AGLKAGERVL VHAATGGVGM AAVQIARHVG AEVFATASPG
3401 KHAVLEEMGI DAAHRASSRD LAFEGTFREA TGGRGMDVVL NSLAGEFIDA
3451 SLRLLGDGGR FLEMGKTDVR AAEEVAAEHA DVSYTAYDLV GDAGPDRISN
3501 MLDKLVELFA SERLKPLPVR SWPLDKAQEA FRFMSQAKHT GKLVLEIPPA
3551 LDPEGTVLVT GGTGALGQVV AEHLVREWGV RHLLLASRRG PEAPGSDELA
3601 SKLTGLGAEV TIVAADVSDP ASVVELVGKT DPSHPLTGVV HAAGVLEDGV
3651 VTAQTPEGLA RVWAAKAAAA ANLHEATREM RLGLFVVFSS AAATLGSPGQ
3701 ANYAAANAYC DALMQHRRAV GQVGLSVGWG LWEAPDAKPG VAADAKASAA
3751 TVGKASALSD GTNGSAPQDT TGTAPQGMTG GLTDTDVARM ARIGVKGMSN
3801 AHGLALFDAA HRHGRPHLVG FNLDLRTLAT HPLHTRPALL RGLATPTAGG
3851 ASRPTATAGG QPADLAGRLA ALSPSDRHHT LVRLIREQAA TVLGHHPDSL
3901 TTGSTFKELG FDSLTAVELR NRLSAATGLR LPAGLVFDHP DADILAEHLG
3951 AQLAPDGDTP AGAEATDPVL RDLAKLENAL SSTLVEHLDA DAVTARLEAL
4001 LSNWKAASAA PGSGSTKEQL QVATTDQVLD FIDKELGV*

MonAV, polyketide synthase multi-enzyme MONS5, housing extension modules 7 and 8 Length: 4107 amino acids

1 MASEEELVDY LKRVAAELHD TRQRLREVED RRQEPVAVVG MACRFPGGIE
51 TPEGLWELVA AGDDAIEPFP TDRGWDLEGI YHPDPDHPGT CYVREGGFLA
101 APDRFDSDFF GFSPREALAS SPQLRLLLET SWEALERAGI NPASLKGSPT
151 GVYVGAATTG NQTQGDPGGK ATEGYAGTAP SVLSGRLSFT LGLEGPAVTV
201 ETACSSSLVA MHLAANALRQ GECDLALAGG VTVMSTPEVF TGFSRQRGLA
251 PDGRCKPFAA AADGTGWGEG AGLILLERLS DARRKGHKVL AVIRGSAINQ
301 DGASNGFTAP NGPSQRRVIR QALSSAHLST SEIDVVEAHG TGTRLGDPIE
351 AEALIATYGK EREDDRPLWL GSVKSNIGHT QAAAGVAGVI KMVMALQREL
401 LPATLNVDEP TPHVQWEGGG VRLLTEPVPW SRGERPRRAG ISSFGISGTN
451 AHVVLEEAPP EEDVPGPVAA EPEGVVPWVV SARTEEALSE QARRLGEFVA
501 DTDPSTADVG WSLTTSRAIL EHRAVVVGRD RDALTAGLAA LAAGEESADV
551 VAGVAGDVGP GPVLVFPGQG SQWVGMGAQL LDESPVFAAR IAECEQALSA
601 YVDWSLSAVL RGDGSELSRV EVVQPVLWAV MVSLAAVWAD YGVTPAAVIG
651 HSQGEMAAAC VAGALSLEDA ARVVAVRSDA LRQLMGQGDM ASLGASSEQA
701 AELIGDRPGV CIAAVNGPSS TVISGPPEHV AAVVADAEER GLRARVIDVG
751 YASHGPQIDQ LHDLLTDRLA DIRPATTDVA FYSTVTAERL TDTTALDTDY
801 WVTNLRQPVR FADTIDALLA DGYRLFIEAS AHPVLGLGME ETIEQADIPA
851 TVVPTLRRDH GDTTQLTRAA AHAFTAGATV DWRRWFPADP TPRTIDLPTY
901 AFQRRSYWLP VDGVGDVRSA GLRRVEHSLL PAALGLADGA LVLTGRLAAS
951 GGGGGWLADH AVAGTTLVPG AALVEWALRA ADEAGCPSLE ELTLQAPLVL
1001 PGSGGLQVQV VVGPADGQGG RREVRVFSRV DSDDEAAGQD EGWSCHATGV
1051 LSPEPGAVPD GLSGQWPPTG AEPLEISDLY EQAASAGYEY GPSFRGLRSV
1101 WRHGHNLLAE VELPEQAGAH DDFGIHPVLL DAALHPALLL DQNAPGEEQE
1151 PAQPALRLPF VWNGVSLWAT GAATVRVRLA PHGGGETDDS AGLRVTVADA

1201 TGAPVLSVDS LALRPADPEL LRTAGRAGSG TNGLFTVEWT ALPPADVADH
1251 AAGDGWAVLG QDVPDWAGAD MPRHPDMASL SAALDEGTQA PAAVFVETTA
1301 TSHATPNTAA DVTLDASGRA VAERTLHLLR DWLAEPRLAE TRLVLITHHA
1351 VTTPADDDVN AAPLDVPAAA LWGLIRSAQA EHPDRFVLLD TDAKANTDPG
1401 PDTSTDHSTA SGTYRTVIAR ALATGEPQLA VRAGELLAPR LARAATPTPE
1451 TPTPETQPDT GSGSEAGAGS GSGPGATLDP DGTVLIAGGT GMMGGLVAEH
1501 LVRAWSVRHL LLVSRQGPDA PDARDLADRL VGLGATVRIV AADLTDGRAT
1551 ADLVASVDPA HPLTGVIHAA GVLDDAVVTA QTSDQLARVW AAKASVAANL
1601 DAATSELPLG LFLMFSSAAG VLGNAGQAGY AAANAFVDAL VGRRRATGLP
1651 GLSIAWGLWA RGSAMTRHLD DADLARLRAG GVKPLLDEQG LALLDAARAT
1701 AAHTSLVVAA GIDVRGLNRD DVPAILRDLA GRTRRRAAAD STVDQAALER
1751 RLTGLDEAER RAVVTDVVRE CVAAVLGHRS AADVRTEANF KDLGFDSLTA
1801 VQLRNRLSAA SGLRLPATLA FDHPTPQALA AYLGTRLSGR TATPVAPVAP
1851 SAAATDEPVA IVAMACKYPG GATSPEGLWD LVAEGVDAVG AFPTGRGWDL
1901 ERLFHPDPDH PGTSYADEGA FLPDAGDFDA AFFGINPREA LAMDPQQRLL
1951 LEASWEVLER AGIDPTTLKG TPTGTYVGVM YHDYAAGLAQ DAQLEGYSML
2001 AGSGSVVSGR VAYTLGLEGP AVTVDTACSS SLVSIHLAAQ ALRQGECTLA
2051 LAGGVTVMAT PEVFTGFSRQ RGLAPDGRCK PFAAAADGTG WGEGVGVLLL
2101 ERLSDARRHG RRVLGVVRGS AVNQDGASNG LTAPNGPSQE RVIRQALASG
2151 GLSSVDVDVV EGHGTGTTLG DPIEAQALLA TYGQGRPVDR PLWLGSVKSN
2201 IGHTQAAAGV AGVIKMVMAM RHGVVPASLH VDVPSPHVEW DSGAVRLAVE
2251 SVPWPEVEGR PRRAGVSSFG ASGTNAHVIV ESVPDGLGED SVSVSGEAPE
2301 TETDGRLVPW VVSARSPQAL RDQALRLRDA VAADSTVSVQ DVGWSLLKTR
2351 ALFEQRAVVV GRERAELLSG LAVLAAGEEH PAVTRSREDG VAASGAVVWL

2401 FSGQGSQLVG MGAGLYERFP VFAAAFDEVC GLLEGPLGVE AGGLREVVFR
2451 GPRERLDHTM WAQAGLFALQ VGLARLWESV GVRPDVVLGH SIGEIAAAHV
2501 AGVFDLADAC RVVGARARLM GGLPEGGAMC AVQATPAELA ADVDDSGVSV
2551 AAVNTPDSTV ISGPSGEVDR IAGVWRERGR KTKALSVSHA FHSALMEPML
2601 AEFTEAIREV KFTRPKVSLI SNVSGLEAGE EIASPEYWAR HVRQTVLFQP
2651 GIAQVASTAG VFVELGPGPV LTTAAQHTLD DVTDRHGPEP VLVSSLAGER
2701 PEESAFVEAM ARLHTAGVAV DWSVLFAGDR VPGLVELPTY AFQRERFWLS
2751 GRSGGGDAAT LGLVAAGHPL LGAAVEFADR GGCLLTGRLS RSGVSWLADH
2801 VVAGAVLVPG AALVEWALRA GDEVGCVTVE ELMLQAPLVV PEASGLRVQV
2851 VVEEAGEDGR RGVQIYSRPD ADAVSGDDSW ICHATGTLTP QHTDAPNDGL
2901 AGAWPAAGAV PVDLAGFYER VADAGYAYGP GFQGLRAVWR HGQDLLAEVV
2951 LPEAAGAHDG YGIHPALLDA TLHPALLLDW PGEVQDDDGK VWLPFTWNQV
3001 SLRAAGAATV RVRLSPGEHD EAEREVQVLV ADATGTDVLS VGSVTLRPAD
3051 IRQLQAVPGH DDGLFSVDWT PLPLSRTDVS QTDADGDADW VVLSDGVGSL
3101 ADVVSAAGGE APWAVVAPVG ASAGGGLAGF DRREGLDGRL VVERVLSLVQ
3151 EFLAAPELAE SRLLVLTRGA VATGGDGDGD VDASAAAVWG LVRSAQSENP
3201 GRFILLDVDM DVDVDVDMDV DVDVDVDVDV DGDGNGSDLD PDLNGRRLPH
3251 ATLRHAAEEL DEPQLALRDG QLLVPRLVRA TGGGLVVAPT DRAWRLDKGS
3301 AETLESVAPV AYPGVMEPLG PGQVRLGIHA AGINFRDVLV SLGMVPGQVG
3351 LGGEGAGVVT ETGPDVTHLS VGDRVMGVLH GSFGPTAVAD TRMVAPVPQG
3401 WDMRQAAAMP VAYLTAWYGL VELAGLKAGE RVLIHAATGG VGMAAVQIAR
3451 HLGAEVFATA SAAKHVVLEE MGIDAAHRAS SRDLAFEDTF RQATDGRGMD
3501 VVLNSLTGEF IDASLRLLGD GGRFLEMGKT DVRTPEEVAA EYPGVTYTVY
3551 DLVTDAGPDR IAVMMSELGE RFASGALDPL PVRSWPLDKA REAFRFMSQA

3601 KHTGKLVLDV PAPLDPDGTV LITGGTGALG QVVAEHLVRE WGVRHLLLAS
3651 RRGLDAPGSG ELADRLSDLG AEVTVAAADV SDPASVVELV GKTDPSHPLT
3701 GVVHAAGVLE DGIVTAQTPE GLARVWAAKA AAAANLHEAT REMRLGLFVV
3751 FSSAAATLGS PGQANYAAAN AYCDALMQRR RAAGQVGLSV GWGLWEAPDA
3801 KPGVAADAKP DVAADAKTGV AADGTPQGMT GTLSGTDVAR MARIGVKAMT
3851 SAHGLALLDA AHRHGRPHLV AVDLDTRVLA HKPAPALPAL LRAFAGDQGG
3901 QGGGRGGGRG GGPARPAAAT TRQNVDWAAK LSVLTAEEQH RTLLDLVRTH
3951 AAAVLGHAGT DAVRADAAFQ DLGFDSLTAV ELRNRLSAST GLRLPATFIF
4001 RHPTPSAIAD ELRAQLAPAG ADPAAPLFGE LDKLETVITG HAHDESTRTR
4051 LAARLQNLLW RLDDTSARSD HAAGASDADG DAVENRDLES ASDDELFELI
4101 DRELPS*

MonAVI, polyketide synthase multi-enzyme MONS6, housing extension module 9 Length: 1701 amino acids

1 MPGTNDMPGT EDKLRHYLKR VTADLGQTRQ RLRDVEERQR EPIAIVAMAC
51 RYPGGVASPE QLWDLVASRG DAIEEFPADR GWDVAGLYHP DPDHPGTTYV
101 REAGFLRDAA RFDADFFGIN PREALAADPQ QRVLLEVSWE LFERAGIDPA
151 TLKDTLTGVY AGVSSQDHMS GSRVPPEVEG YATTGTLSSV ISGRIAYTFG
201 LEGPAVTLDT ACSASLVAIH LACQALRQGD CGLAVAGGVT VLSTPTAFVE
251 FSRQRGLAPD GRCKPFAEAA DGTGFSEGVG LILLERLSDA RRNGHQVLGV
301 VRGSAVNQDG ASNGLTAPND VAQERVIRQA LTNARVTPDA VDAVEAHGTG
351 TTLGDPIEGN ALLATYGKDR PADRPLWLGS VKSNIGHTQA AAGVAGVIKM
401 VMAMRHGELP ASLHIDRPTP HVDWEGGGVR LLTDPVPWPR ADRPRRAGVS
451 SFGISGTNAH LIVEQAPAPP DTADDAPEGA ATPGASDGLV VPWVVSARSP
501 QALRDQALRL RDFAGDASRA PLTDVGWSLL RSRALFEQRA VVAGRERAEL
551 LAGLAALAAG EEHPAVTRSR EEAAVAASGD VVWLFSGQGS QLVGMGAGLY

601 ERFPVFAAAF DEVCGLLEGE LGVGSGGLRE VVFWGPRERL DHTVWAQAGL
651 FALQVGLARL WESVGVRPDV VLGHSIGEIA AAHVAGVFDL ADACRVVGAR
701 ARLMGGLPEG GAMCAVQATP AELAADVDGS SVSVAAVNTP DSTVISGPSG
751 EVDRIAGVWR ERGRKTKALS VSHAFHSALM EPMLGEFTEA IRGVKFRQPS
801 IPLMSNVSGE RAGEEITSPE YWARHVRQTV LFQPGVAQVA AEARAFVELG
851 PGPVLTAAAQ HTLDHITEPE GPEPVVTASL HPDRPDDVAF AHAMADLHVA
901 GISVDWSAYF PDDPAPRTVD LPTYAFQGRR FWLADIAAPE AVSSTDGEEA
951 GFWAAVEGAD FQALCDTLHL KDDEHRAALE TVFPALSAWR RERRERSIVD
1001 AWRYRVDWRR VELPTPVPGA GTGPDADTGL GAWLIVAPTH GSGTWPQACA
1051 RALEEAGAPV RIVEAGPHAD RADMADLVQA WRASCADDTT QLGGVLSLLA
1101 LAEAPATSSD TTSHTSTSCG TGSLASHGLT GTLTLLHGLL DAGVEAPLWC
1151 ATRGAVSCGD ADPLVSPSQA PVWGLGRVAA LEHPELWGGL VDLPADPESL
1201 DASALYAVLR GDGGEDQVAL RRGAVLGRRL VPDATPDVAP GSSPDVSGGA
1251 AHADATSGEW QPHGAVLVTG GVGHLADQVV RWLAASGAEH VVLLDTGPAN
1301 SRGPGRNDDL AAEAAEHGTE LTVLRSLSEL TDVSVRPIRT VIHTSLPGEL
1351 APLAEVTPDA LGAAVSAAAR LSELPGIGSV ETVLFFSSVT ASLGSREHGA
1401 YAAANAYLDA LAQRAGADAA SPRTVSVGWG IWDLPDDGDV ARGAAGLSRR
1451 QGLPPLEPQL ALGALRAALD GGKGHTLVAD IEWERFAPLF TLARPTRLLD
1501 GIPAAQRVLD ASSESAEASE NASALRRELT ALPVRERTGA LLDLVRKQVA
1551 AVLRYEPGQD VAPEKAFKDL GFDSLVVVEL RNRLRAATGL RLPATLVYDY
1601 PTPRTLAAHL LDRVLPDGGA AELPVAAHLD DLEAALTDLP ADDPRRKGLV
1651 RRLQTLLWKQ PDAMGAAGPA DEEEQAAPED LSTASADDMF ALIDREWGTR
1701 *

MonH, probable regulatory protein Length: 981 amino acids

1 VSGVERGVGS AGPVEQGDGL AGLVERAEAL AALRGAFDGS PGTGGSLVVL

51 SGAVGTGKTA LLRAWADRIG ADADALVLTA TACRAERDLP LGVLEQLVRS

101 PGLPPASAER ALAWWDEEAS ATPGKTDANG TSANGTDANG TGAGQTGAGQ

151 AGVGQTGVGG EPVLAASALR GLCEVLRDLL AERPVVVAVD DAHHADAASL

201 QCLLSVVRRL RSARLHVLFT EYAHQKAQNA LLSSEFLHEP ALRRIRLEPL

251 SKAGVEALLA RHLDERTAQD LTPVVHGMSA GHPLLVRALA EDHRAAGGAG

301 EAYGRAVLSF LYRHETPVTQ VARAIAALGA HAGPGQVGRL LDVDAASVER

351 AVRQLTVAEV LHEGRLCHPA FAAAVLDGMP PEERRALHGR VADLLHEEGA

401 PATEVAAHLV AADRSDAPWA VPVFQEAAQL ALDEDQVETG VDYLRAAHQR

451 CRGAAQRAAV VGALADAEWR LDPAKVLRHL PDPAAMAPQT DPAALAPHTD

501 PAPTAAPTAA PTPTPIPTTP PLPTHLLWHG RVEEGLDAIG TLTGPGPNPA

551 GAPPMNPADL DTPWLWGAYL YPGHVKERLG SGALSPQRST PPAVTPELQG

601 AGTLMNDLLH GGERDATEAA ERALNRYRLG PRTIAVQTAA LAALTYRDRP

651 HRAAAWCDGL VAQADERNSP TWRALFTAWR ALLHLRQGDP AAAEQRAETA

701 LALLGSKGWG AAIGLPLAAA VQAKAALGDV DGAAALLERP VPQAVFQTRT

751 GLHYLAARGR YHLATGCHYA ALCDFYACGT RMSSWGVDLP ALEPWRLGAA

801 EAYLALGEGL LARQLVDGQL PLPTPDDGRT WGMTLRLRAA TSPAPARAEL

851 LDEAVAVLRE SGDTFELARA VADQAVAVRE GGEAERARLL ARKAELLARR

901 WGSAPAPATV PEPPERPGPA TPDAELTSAE RRVAELAAEG FTNREISRKL

951 CVTVSTVEQH LTRIYRKLDV RRLDLQAALG *

MonCI, flavin-dependent epoxidase Length: 496 amino acids

1 VTTTRPAHAV VLGASMAGTL AAHVLARHVD AVTVVERDAL PEEPQHRKGV

51 PQARHAHLLW SNGARLIEEM LPGTTDRLLA AGARRLGFPE DLVTLTGQGW

101 QHRFPATQFA LVASRPLLDL TVRQQALGAD NITVRQRTEA VELTGSGGGS

151 GGRVTGVVVR DLDSGRQEQL EADLVIDATG RGSRLKQWLA ALGVPALEED
201 VVDAGVAYAT RLFKAPPGAT THFPAVNIAA DDRVREPGRF GVVYPIEGGR
251 WLATLSCTRG AQLPTHEDEF IPFAENLNHP ILADLLRDAE PLTPVFGSRS
301 GANRRLYPER LEQWPDGLLV IGDSLTAFNP IYGHGMSSAA RCATTIDREF
351 ERSVQEGTGS ARAGTRALQK AIGAAVDDPW ILAATKDIDY VNCRVSATDP
401 RLIGVDTEQR LRFAEAITAA SIRSPKASEI VTDVMSLNAP QAELGSNRFL
451 MAMRADERLP ELTAPPFLPE ELAVVGLDAA TISPTPTPTP TAAVRS

MonBII, carbon-carbon double bond isomerase Length: 141 amino acids

1 MPDEAARKQM AVDYAERINA GDIEGVLDLF TDDIVFEDPV GRPPMVGKDD
51 LRRHLELAVS CGTHEVPDPP MTSMDDRFVV TPTTVTVQRP RPMTFRIVGI
101 VELDEHGLGR RVQAFWGVTD VTMDDPAGPA DTTHPEGIRA *

MonBI, carbon-carbon double bond isomerase Length: 144 amino acids

1 MNEFARKKRA LEHSRRINAG DLDAIIDLYA PDAVLEDPVG LPPVTGHDAL
51 RAHYEPLLAA HLREEAAEPV AGQDATHALI QISSVMDYLP VGPLYAERGW
101 LKAPDAPGTA RIHRTAMLVI RMDASGLIRH LKSYWGTSDL TVLG

MonAVIII, polyketide synthase multi-enzyme MONS8, housing extension modules 11 and 12 Length: 3754 amino acids

1 MSNEEKLLDH LKWVTAELRQ ARQRLHDKES TEPVAIVGMA CRYPGGARSA
51 EDLWELVRDG GDAVAGFPDD RGWDLESLYH PDPEHPATSY VRDGAFLYDA
101 GHFDAEFFGI SPREATAMDP QQRLLLETAW EAIEHAGMNP HALKGSDTGV
151 FTGVSAHDYL TLISQTASDV EGYIGTGNLG SVVSGRISYT VGLEGPAVTV
201 DTACSSSLVA IHLASQALRQ GECSLALAGG STVMATPGSF TEFSRQRGLA
251 PDGRCKPFAA AADGTGWGEG AGVVALELLS EARRRGHKVL AVIRGSATNQ
301 DGTSNGLAAP NGPSQERVIR AALANARLSA EDIDAVEAHG TGTTLGDPIE

351 AQALIATYGQ GRPEDRPLWL GSVKSNIGHT QAAAGVAGVI KMVMAMRNGL
401 LPTSLHIDAP SPHVQWEQGS VRLLSEPVDW PAERTRRAGI SAFGISGTNA
451 HLILEEAPPE EDAPGPVAAE PGGVVPWVVS GRTPDALREQ ARRLGEFAAG
501 LADASVSEVG WSLATTRALF DQRAVVVGRD LAQAGASLEA LAAGEASADV
551 VAGVAGDVGP GPVLVFPGQG SQWVGMGAQL LDESPVFAAR IAECEQALSA
601 HVDWSLSDVL RGDGSELSRV EVVQPVLWAV MVSLAAVWAD YGITPAAVIG
651 HSQGEMAAAC VAGALSLEDA ARIVAVRSDA LRQLQGHGDM ASLSTGAEQA
701 AELIGDRPGV VVAAVNGPSS TVISGPPEHV AAVVADAEAQ GLRARVIDVR
751 YASHGPQIDQ LHDLLTDRLA DIQPTTTDVA FYSTVTAERL DDTTALDTAY
801 WVTNLRQPVR FADTIEALLA DGYRLFIEAS PHPVLNLGIQ ETIEQQAGAA
851 GTAVTIPTLR RDHGDTTQLT RAAAHAFTAG APVDWRRWFP ADPTPRTVDL
901 PTYAFQHKHY WVEPPAAVAA VGGGHDPVEA RVWQAIEDLD IDALAGSLEI
951 EGQAESVGAL ESALPVLSAW RRRHREQSTV DSWRYQVTWK HLPDVPAPEL
1001 SGAWLLLVPA AHADHPAVLA TAQTLTAHGG EVRRHVVDAR AMERTELAQE
1051 LRVLMDGAAF AGVVNLLALD EEPHPEHSAV PAGLAATTAL VQALADNGAD
1101 IAVRTLTQGA VSTSAGDALT HPVQAQVWGL GRVAALEYPR LWGGLVDLPA
1151 RIDHQTLARL AAALVPQDED QISIRPSGVH ARRLAHAPAN TVGSGLGWRP
1201 DGTTLITGGT GGIGAVLARW LARAGAPHLL LTSRRGPDAP GAQELAAELT
1251 ELGAAVTVTA CDVGDREQVR RLIDDVPAEH PLTAVIHAAG VPNYIGLGDV
1301 SGAELDEVLR PKALAAHHLH ELTRELPLSA FVMFSSGAGV WGSGQQGAYG
1351 AANHFLDALA EHRRAEGLPA TSIAWGPWAE AGMAADQAAL TFFSRFGLHP
1401 LSPELCVKAL QQALDAGETT LTVANFDWAQ FTSTFTAQRP SPLLADLPEN
1451 RRASAPAAQQ EDATEASSLQ QELTEAKPAQ QRQLLLQHVR SQAAATLGHS
1501 DVDAVPATKP FQELGFDSLT AVELRNRLNK STGLTLPTTV VFDHPTPDAL

1551 TDVLRAELSG DAAASADPVR AAGASRGAAD DEPIAIVGMA CRYPGDVRSA
1601 EELWDLVAAG KDAMGAFPDD RGWDLETLYD PDPESRGTSY VREGGFLYDA
1651 GDFDAGFFGI SPREAVAMDP QQRLLLETAW EAIERAGLDR ETLKGSDAGV
1701 FTGLTIFDYL ALVGEQPTEV EGYIGTGNLG CVASGRVSYV LGLEGPAMTI
1751 DTGCSSSLVA IHQAAHALRQ GECSLALAGG ATVMATPGSF VEFSLQRGLA
1801 KDGRCKPFAA AADGTGWAEG VGLVVLERLS EARRNGHNVL AVIRGSAINQ
1851 DGTSNGLTAP NGQAQQRVIR QALANARLSA EDVDAVEAHG TGTMLGDPIE
1901 ASALVATYGK ERPADRPLWL GSIKSNIGHA QASAGVAGVI KMVMALRNEQ
1951 LPASLHIDAP TPHVDWDGSG VRLLSEPVSW PRGERPRRAG VSAFGISGTN
2001 AHLILEQAPD APEPVTAPAE DAAAPAGVVP WVVSARGEEA LRAQARLLAD
2051 RATADPRLAS PLDVGWSLVK TRSVFENRAV VVGKDRQTLL AGLRSLAAGE
2101 PSPDVVEGAV QGASGAGPVL VFPGQGSQWV GMGAQLLDES PVFAARIAEC
2151 ERALSAHVDW SLSAVLRGDG SELSRVEVVQ PVLWAVMVSL ASVWADYGIT
2201 PAAVIGHSQG EMAAACVAGA LSLEDAARIV AVRSDALRQL MGQGDMASLG
2251 AGSEQVAELI GDRPGVCVAA VNGPSSTVIS GPPEHVAAVV ADAEARGLRA
2301 RVIDVGYASH GPQIDQLHDL LTERLADIRP TTTDVAFYST VTAERLDDTT
2351 TLDTDYWVTN LRQPVRFADT IEALLADGYR LFIEASPHPV LNLGMEETIE
2401 RADMPATVVP TLRRDHGDAA QLTRAAAQAF GAGAEVDWTG WFPAVPLPRV
2451 VDLPTYAFQR ERFWLEGRRG LAGDPAGLGL ASAGHPLLGA AVELADGGSH
2501 LLTGRISPRD QAWLAEHRVM DTVLLPGSAF VELALQAAVR AGCAELAELT
2551 LHTPLAFGDE GAGAVDVQVV VGSVAEDGRR PVTVHSRPTG EGEEAVWTRH
2601 AAGVVAPPGP DAGDASFGGT WPPPGATPVG EQDPYGELAS YGYDFGPGSQ
2651 GLVSAWRLGD DLFAEVALPE AESGRADRYQ VHPVLLDATL HALILDAVTS
2701 SADTDQVLLP FSWSGLRVHA PGAEKLRVRI ARTAPDQLAL TAVDGGGGGE

2751 PVLTLESLTV RPVAAHQIAG ARAADRDALF RLVWMEVAAR AEETGGGAPR
2801 AAVLAPVESG PMGGTSAGAL ADALSDALAA GPVWDTFGAL RDGVAAGGEA
2851 PDVVLAVCAA PGAGAGAVAD ADGRGGDPAG YARLATVSLL SLLKEWVDDP
2901 AFAATRLVVV TRGAVAARPG ETAGDLAGAS LWGLVRSAQA ENPGRLTLLD
2951 VDGLESSPAT LTGVLASGEP ELALRDGRAY VPRLVRDDAS VRLVPPVGSL
3001 TWRLARCQEA GGGQQLSLVD APEAGRALEP HEVRVAVRAA APGPLTAGQV
3051 EGAGVVTEVG GEVGSVAVGD RVMGLFDAVG PVAVTDAALL MPVPAGWSWA
3101 QAAGSLGAYV SAYHVLADVV APRGGETLLV GEETGSVGRA VLRLALAGRW
3151 RVEAVDGAST ADDSGAERAA DVTLRHEGAL VVHRAGGRPD EGQAVVPPEP
3201 GRVREILAEL TELTELAEIT ESAEPGLPAE RGDSRALTPL DITVWDIRQA
3251 PAAMAAPPSA GTTVFSLPPA FDPEGTVLVT GGTGALGSLT ARHLVERYGA
3301 RHLLLSSRRG ADAPGALELA ADLSALGARV TFAACDPGDR DEAAALLAAV
3351 PSDHPLTAVF HCAGTVNDAV VQNLTAEQVE EVMRVKADAA WHLHELTRDA
3401 DLSAFVLYSS VAGLLGGPGQ GSYTAANAFL DALARHRHDG GAAATSLAWG
3451 YWELASGMSG RLTDADRARH ARAGVVGLGA DEGLALLDAA WAGGLPLYAP
3501 VRLDLARMRR QAQSHPAPAL LRDLVRGGSK SGGGAVSAGA AALLKSLGAM
3551 SDPEREEALL DLVCTHIAAV LGYDAATPVN ATQGLRELGF DSLTAVELRN
3601 RLSAATGLKL PATFVFDHPN PAELAAQLRQ ELAPRAADPL ADVLAEFERI
3651 EDSLLSVSSK DGSARAELAG RLRATLARLD APQDTAGEVA VATRTRIQDA
3701 SADEIFAFID RDLGRDGASG QGNGQPTGQG NGHGNGNGNG NGNGHGQAVE
3751 GQR*

MonAVII, polyketide synthase multi-enzyme MONS7, housing extension module 10 Length: 1642 amino acids

1 MAHTEEKLLE YLKRVTADLR QTERRLQDVE SAGHEPVAVI GMACRLPGGV
51 RSPEEFWELV STGGDAVAPL PGNRNWDLDS LYDPDPESTG TSYVREGGFV

101 YDAGDFDPTF FGIGPTEAAA MAPQQRLALE TAWEAIERAG IDPLSLRSSD

151 TSTFIGCDGL DYALGASEVP EGTAGYFTIG NSGSVTSGRV AYTLGLEGPA

201 VTVDTACSSS LVSLHLATQA LRTQECSLAL AGGTYVMSSP APLIGFSELR

251 GLAPDGRCKP FSASSDGMGM AEGTGVVLLE RLSDARRKGH KVLAVIRGSA

301 INQDGASNGL TAPNGPAQER VIRAALANAR LAPEDIDAVE AHGTGTTLGD

351 PIEAGALISA YGRERPEDRP LWVGAVKSNI GHTQIAAGVA GVIKMVLALR

401 HDLLPAILHV DAPSPHVEWD GSGLRLLTDP VKWPRGERPR RAGVSSFGFS

451 GTNAHLILEE APPEEEDVPG SVAEEPGGVV PWVVSGRTPD ALRAQARRLG

501 EFAAGPADAS AADVGWSLTT TRSVFEHRAV VVGRDRDALT AGLGALAAGE

551 ASAGVVAGVA GDVGPGPVLV FPGQGSQWVG MGAQLLDESP VFAARIAECE

601 RALSAYVDWS LSAVLRGDGS ELSRVEVVQP VLWAVMVSLA AVWADYGVTP

651 AAVIGHSQGE MAAACVAGAL SLEDAARIVA VRSDALRRLQ GHGDMASLST

701 GAEQAAELIG DRPGVVVAAV NGPSSTVISG PPEHVAAVVA DAEARGLRAR

751 VIDVGYASHG PQIDQLHDLL TERLADIRPA NTDVAFYSTV TAERLTDTTA

801 LDTDYWVTNL RQPVRFADTI EALLADGYRL FIEASAHPVL GLGMEETIEQ

851 ADIPATVVPT LRRDHGDTTQ LTRAAAHAFT AGAPVDWRRW FPADPTPRTV

901 DLPTYAFQHQ HYWLERSASA SGAVSGEQSA AEAQLWHAVE ELDLGLLAET

951 LGSEEGSEEA VRALEPALPV LKGWRRRHQD QATIDSWRYR VTWKQRSDGP

1001 APELGGDWLL FVPADKAEHP AVRATAEALS EHGAAAVRLH PVETGRAGRQ

1051 ELAAVDTAGL AGIVNLLALD EEPHPEHPAV PAGLAATTAL LQALGDNGTT

1101 APLHTVTQGA VSTGATDPLT HPLQAHVWGL GRVAALEHPR LWAGLVDLPA

1151 RIDRHTLPRL AAALLPQDDE DQTAVRPTGI HHRRLTHAVG SIQNPVHSEA

1201 TWRPRGTTLI TGGTGGIGAV LARWLARQGA PRLHLTSRRG PDAPGARELA

1251 AELDGLGTAV TITACDVSDP RQLSGLIDDM PAEHPLTAVI HAAGMTDLTA

1301 IGDLTTARLG EVLGSKSDAA WNLHELTRDL DLSAFVMFSS GAGVWGSGQQ

1351 GAYGAANHFL DALAEHRRAQ GLPATSIAWG PWAEAGMSAD PESLTYFKRF

1401 GLLPIAPDLC VKALHQAVDA GDATLTVANF DWAKFTPTFT AQRPSPFLDD

1451 LPENQREAEQ TGTAAETSAF REELAKTPAS QRLGFLVQQV RTYAAATLGR

1501 TVEDIPAAKP FQELGFDSLT AVQLRNQLNT TTGLSLPATV IFDHPTPEAL

1551 ATHLRGQLGD GAEVAGEGDV LAALDKWDTA FGAAEVDEAA RRRIVGRLQV

1601 LVSKWSPAQD GPEGTDSAHA DLEAASADDI FDLISSEFGK S*

MonD, cytochrome P450 hydroxylase Length: 431 amino acids

1 VGLTVGPDNA KRGIVPITDS KPAATFPDLV DPSFWARPHA ERVALFEEMR

51 GLPRPAFIRQ NMPGVPWTFG YHALVKYADI VEVSRRPQDF SSNGATTIIG

101 LPPELDEYYG SMINMDNPEH SRLRRIVSRS FGRNMIPEFE AVATRTARRI

151 IDELIARGPG DFIRPVAAEM PIAVLSDMMG IPAEDHDFLF DRSNTIVGPL

201 DPDYVPDRAD SERAVIEASR ELGDYIAGLR AERLAAPGND LITKLVQVQA

251 DGEQLTRQEL VSFFILLVIA GMETTRNAIS HALVLLTEHP EQKQLLLSDF

301 DTHAPNAVEE ILRVSTPINW MRRVATRDCD MNGHRFRRGD RIFLFYWSGN

351 RDESVFPDPY RFDITRGTNA HVTFGAVGPH VCLGAHLARM EITVLYRELL

401 AALPQIHAVG QPRRLDSSFI EGIKHLHCAF *

MonRI, probable activator protein Length: 268 amino acids

1 VRYEMLGPLR IKDGNDYATI NAQKVEIVLT VLLIRADRVV SLEQLMREIW

51 GEDLPRRATA GLHVYISQLR KFLKVPGSAG NPVETRAPGY VLHKRDDDQI

101 DAQIFPELVD VGRSLLREKR FDEAASCFGQ ALALWRGPIL GQGGNGPGTN

151 GPIIDGFSTW LTEIRLECQE MLVECQLQLG RHREAVGMLY ALTAENPMCE

201 AFYRQLMLAL YRSERQADAL KVYQSVRKTL NDELGLEPGR PLQELQRAIL

251 AGDMHLMSPP PLALSGR*

MonAX, thioesterase Length: 278 amino acids

1 LSAFLAKGKI LSAFPPPDMS DPWIRRFRPR PEAVVRLVCF PHAGGSASYY

51 HPLAQSPTLP TDSEVLAVQY PGRQDRRRER LLDDIGELAD LITDALGPFD

101 DRPLAFFGHS MGAVLAYEVA QRLRERTGKQ PCRLFVSGRR APSRFRRGTV

151 HLLDDTELAA ELRRAGGTDP RFLDDEELLA EIIPVVRNDY RAVELYRWNP

201 SPPLSCPITA LVGDRDPQAP LDEVEAWQQH TEGPFDLKVF AGGHFYLNTH

251 QQGVTEVISK ALADSAQQRA TARGNAR*

ORF29, a homologue of CapK involved in cell wall biosynthesis Length: 428 amino acids

1 LADLVAHARS ASPYYRELYH GLPERIEDPT LLPVTDKKQL MDHFDDWPTD

51 RDITFEKVRA FTDDPELIGR RFLGRYLVAT TSGTSGRRGL FVLDDRYMNV

101 SSAVSSRVLA SWLGPLGIAR AVVHGGRFAQ LVATEGHYVG FAGYSRLRQD

151 GEARSKLVRA FSVHEPMSRL VAELNEYRPA FVIGYASTIM LFTAEQEAGR

201 LHIDPVLVEP AGETMTESDT DRIAAAFGAK VRTMYSATEC TYLSHGCAEG

251 WYHVNDDWAV LEPVDADHRP TPPGEFSHTT LISNLANRVQ PFLRYDLGDS

301 VMLRPDPCPC GTPSPAIRVQ GRSGDILTFP SGRGDDVSLA PLAFSSLFDR

351 MPGVELFQIE QTAPSTLRVR VVQAPGADAD HVWQRAHDGL THLLADNKLD

401 NVTVERGEEP PRQASGGKYR TIIPLAA*

LipB, lipase B Length: 338 amino acids

1 VKVPVEVTVR LSSWLGGLVA AVLAATVLPA SAASAADVSS PPLEIPAAEL

51 AKALHCGTEL GDLRDAGDKP TVLFVPGTGL KGEENYAWNY MAELKKKGYQ

101 SCWVDSPGRG LRDMQESVEY VVYATRAIQE ATGRKVDLVG HSQGGLLTAW

151 ALRFWPDLPG KVDDMVTLGS PFQGTRLASP CRPIAEVAGC PASVLQFARD

201 SNWSKALGAD GTPMPAGPSY TTIYSYADES VVADGEAPSL PGAHRIGVQD

251 ICPGRPWPTH IAMVVDQVSY DLVADAIEHP GPADTSRIDR AHCAKPVMPL

301 NSQEAVDALP GLLNFPIELL IHSQPWVDEE PPLRPYAR

ORF31, putative ion pump Length: 309 amino acids

1 MGHDHGPSAG AAGGTLSGTY RKRLLWTIGI SGSITVIQVV GALLSGSLAL

51 LADAAHSLTD AVGVSLALGA ITLAQRAPTP RRTFGFCRVE IFSAVLNALL

101 LVVIFAWVLW SAIGRFSEPV EVKGGLMFVV ALGGLAANLV GLWLLRDAKE

151 KSLNLRGAYL EVLGDALGSV AVIVGGLVIL LTGWQAADPI ASIVIGLLIV

201 PRAYGLLRDS LHVLLEATPQ DVDLGEVRRH LLEERGVVAV HDLHGWTVTS

251 GMPVLTAHVV VTEEALASGY GELLGRLQRC VGGHFDVAHS TIQLEPEGHV

301 EEDGALHT*

ORF32, hypothetical membrane protein Length: 364 amino acids

1 MTRALTLHDW IVAGIAVVAG VVAGLLLRAL LRWLGERASK TRWSGDDVIV

51 DALRTLVPCA AITAGLAAAA GALPLTPRTG RNVTMTLTAL LILAATLTAA

101 RIVTGLVKAV AQSRSGVAGS ATIFVNITRV VVLAMGFLIV LQTLGISIAP

151 LLTALGVGGL AVALALQDTL ANLFAGVHIL AAKTVQPGDY IQLSSGEEGY

201 VVDINWRNTT VRQLSNNLVI IPNAKLAGTN MTNYSRPEQE LSIMVQVGVS

251 YDSDLEQVEK VTTEVVDEVM AEITGAVPDH EAAIRFHTFG DSRISFTVIL

301 GVGEFSDQYR IKHEFIKRLH QRYRAEGIRV PAPVRTVRVQ QGELPPPLGI

351 PHQRDTSTQA RLH*

AmtA, glycine amidinotransferase (partial coding sequence) Length: 131 amino acids

1 MSPVNSHNEW DPLEEIIVGR LEGATIPSSH PVVACNIPTW AARLQGLAAG

51 FEYPQRLIEP AQQELDQFIA LLQSLDVTVR RPAAVDHKHR FGTPDWQSRG

101 FCNSCPRDSM LVVGDEIIET PMAWPCRCFE T

CLAIMS:

1. A DNA sequence which is (a) at least part of the sequence set out in the appended sequence listing; or (b) a variant of a sequence (a) which encodes a polypeptide which is at least 80%, preferably at least 90%, identical with the corresponding peptide as set out in table II; provided that it is not a sequence encoding all or part of the polypeptide consisting of amino acids 1-920 encoded by *mon AI* as set out in table II.

2. A DNA sequence according to claim 1 comprising the complete monensin gene cluster or a variant thereof.

3. A DNA sequence encoding at least part of at least one polypeptide which is necessary for the biosynthesis of monensin, and which is encoded by DNA included in the appended sequence listing or an allele, mutation or other variant thereof; provided that said polypeptide is not all or part of amino acids 1-920 encoded by *mon AI* as set out in table II.

4. A DNA sequence according to claim 3 which comprises at least part of one or more of the following genes: *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX*.

5. A DNA sequence according to claim 4 comprising all of the genes listed therein or an allele, mutation or other variant thereof.

6. A DNA sequence according to claim 3 encoding at least part of one or more of the polypeptides set out below, said polypeptide having the amino acid sequence as set out in the appended sequence data or being a variant thereof having the specified activity:

<u>peptide</u>	<u>activity</u>
mon CII	epoxyhydrolase/cyclase
mon E	S-adenosylmethionine-dependent methyltransferase
mon T	monensin resistance gene
mon RII	repressor protein
mon AIX	thioesterase
mon AI	polyketide synthase multienzyme
mon AII	polyketide synthase multienzyme
mon AIII	polyketide synthase multienzyme
mon AIV	polyketide synthase multienzyme
mon AV	polyketide synthase multienzyme
mon AVI	polyketide synthase multienzyme
mon AVII	polyketide synthase multienzyme
mon AVIII	polyketide synthase multienzyme
mon H	regulatory protein
mon CI	flavin-dependent epoxidase
mon BII	carbon-carbon double bond isomerase

mon BI	carbon-carbon double bond isomerase
mon D	cytochrome P450 hydroxylase
mon RI	activator protein
mon AX	thioesterase

7. A DNA sequence according to claim 6 encoding a single enzyme activity of a multienzyme encoded by any of *mon AI-mon AVIII* or a variant or part thereof.

8. A DNA sequence according to any preceding claim encoding any one or more of the domains as set out in Table I or a variant or part thereof.

9. A DNA sequence according to any preceding claim which has a length of at least 30, preferably at least 60, bases.

10. A recombinant cloning or expression vector comprising a DNA sequence according to any preceding claim.

11. A transformant host cell which has been transformed to contain a DNA sequence according to any of claims 1-9 and which is capable of expressing a corresponding polypeptide.

12. A hybridisation probe which is a DNA sequence according to any of claims 1-9.

13. Use of a probe according to claim 12 to detect a PKS cluster, optionally followed by isolation of the detected cluster.

14. Use of a probe according to claim 12 which encodes at least part of a polypeptide having a known function to detect genes encoding polypeptides having analogous function.

15. Use according to claim 14 wherein the polypeptide of known function is AT of module 5 or the regulatory protein encoded by *mon RI*.

16. A hybridization probe comprising a polynucleotide which binds specifically to a region of the monensin gene cluster selected from *mon BI, mon BII, mon CI, mon CII, mon H, mon RI, mon RII, mon T, mon AIX* and *mon AX*.

17. Use of a probe according to claim 16 in a method of detecting the presence of a gene cluster which governs the synthesis of a polyether, and optionally isolating a gene cluster detected thereby.

18. Use of a probe according to claim 12 which comprise a polynucleotide which binds specifically to a gene responsible for levels of activity of the monensin gene cluster, in a method of detecting an analogous gene in a gene cluster for biosynthesis of another polyketide, optionally followed by a step of manipulating the gene detected thereby to alter the level of expression of said other polyketide.

19. Use according to claim 18 wherein the gene is a regulatory gene, resistance gene or thioesterase gene.

20. Use of the *mon RI* gene or variant and a monensin promoter to control expression of a heterologous gene in *S. cinnamonensis*.

21. Use of a portion of the monensin gene cluster encoding a polypeptide having chain terminating activity, preferably comprising at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof encoding a polypeptide having chain terminating activity, to effect chain release of a peptide other than monensin.

22. Use of a portion of the monensin gene cluster encoding a polypeptide having carbon-carbon double bond isomerase activity, preferably comprising at least one of

mon BI and *mon BII* or a mutant, allele or other variant thereof having isomerase activity to provide a desired stereochemical outcome in the synthesis of a polyketide other than monensin.

23. A polypeptide encoded by a portion of the monensin gene cluster, preferably comprising at least one of *mon BI* and *mon BII* or a mutant, allele or other variant thereof, having carbon-carbon double bond isomerase activity, or at least one of *mon AIX* and *mon AX* or a mutant, allele or other variant thereof having chain terminating activity.

24. An epoxidase enzyme encoded by *mon CI* or a derivative or variant thereof having epoxidase activity.

25. A cyclase enzyme encoded by *mon CII* or a derivative or variant thereof having cyclase activity.

26. Use of a portion of the monensin gene cluster encoding a peptide having epoxidase or cyclase activity, preferably comprising *mon CI* or *mon CII* or a mutant, allele or other variant thereof encoding a polypeptide having epoxidase or cyclase activity to provide a said activity in the biosynthesis of a polypeptide other than monensin.

27. A process for producing a polyketide containing a desired starter unit comprising providing a PKS gene having a loading module and a plurality of extension modules, wherein the loading module includes a KS_q domain derived from a KS domain of a monensin extension module.

28. A process according to claim 27 wherein the KS_q domain is derived from KS of module 5 of monensin.

29. A process according to claim 27 or claim 28 wherein the starter unit also includes an AT_q domain derived from an AT domain which is naturally associated with the KS domain.

30. A DNA sequence comprising DNA encoding at least one PKS loading module and a plurality of PKS extension modules, and which can be expressed to produce a polyketide; wherein at least one of said modules or at least one domain thereof is a monensin module or domain or a variant thereof and is contiguous to a further one of said modules or a domain to which it is not naturally contiguous; provided that the sequence is not an ery loading module, the first and second extension modules of the ery PKS and the ery chain-terminating thioesterase in which the DNA encoding AT of the first extension module has been substituted by DNA encoding an ethyl malonyl-CoA

AT from the monensin gene cluster.

31. A DNA sequence according to claim 30 wherein said further module or domain is also a monensin module or domain or variant thereof.

32. A DNA sequence according to claim 30 wherein said further module or domain is a module or domain of a PKS of a polyketide other than monensin or a variant thereof.

33. A DNA sequence according to claim 30, 31 or 32 wherein said loading module is adapted to load a starter unit other than a starter unit normally received by the adjacent extension module.

34. A DNA sequence according to claim 33 wherein said loading module is derived from a monensin extension module or variant thereof.

35. A polyketide synthase encoded by the DNA sequence of any of claims 30-34.

36. A polyketide compound as produced by a synthase according to claim 35.

37. A vector containing a DNA sequence of any of claims 30-34.

38. A transformant cell transformed to contain a DNA sequence of any of claims 30-34.

39. A method of producing *S. cinnamonensis* capable of enhanced levels of production of monensin comprising engineering it to overexpress the *mon RI* gene.

40. A method according to claim 39 wherein said engineering comprises introducing at least one additional copy of the *mon RI* gene as shown in the appended sequence data or a variant thereof.

41. *S. cinnamonensis* containing multiple copies of the *mon RI* gene as shown in the appended sequence data and/or variant(s) thereof.

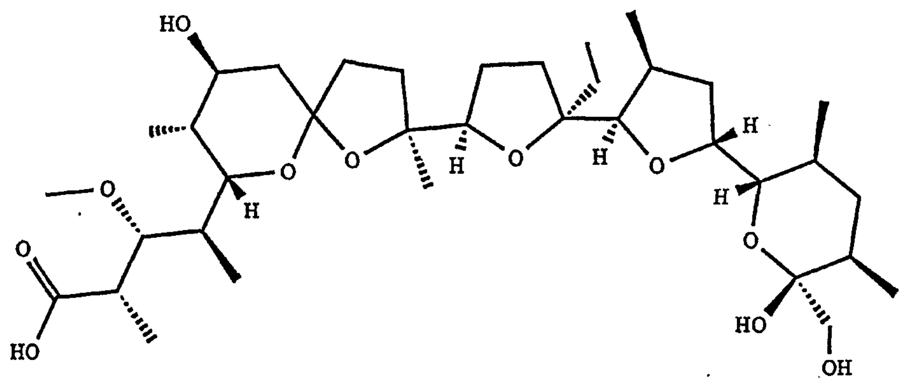
42. A method of producing monensin comprising culturing the organism of claim 41 and/or an organism produced by the method of claim 39 or claim 40.

43. A process for expressing a gene heterologous to *S. cinnamonensis* comprising transforming *S. cinnamonensis* with DNA encoding a heterologous gene and expressing said

gene under control of the activator gene *mon RI* or actII/orf4.

44. A process according to claim 43 wherein said heterologous gene is a PKS gene.

45. 13-Propyl erythromycin A.



monensin A : R = ethyl
monensin B : R = methyl

Fig 1

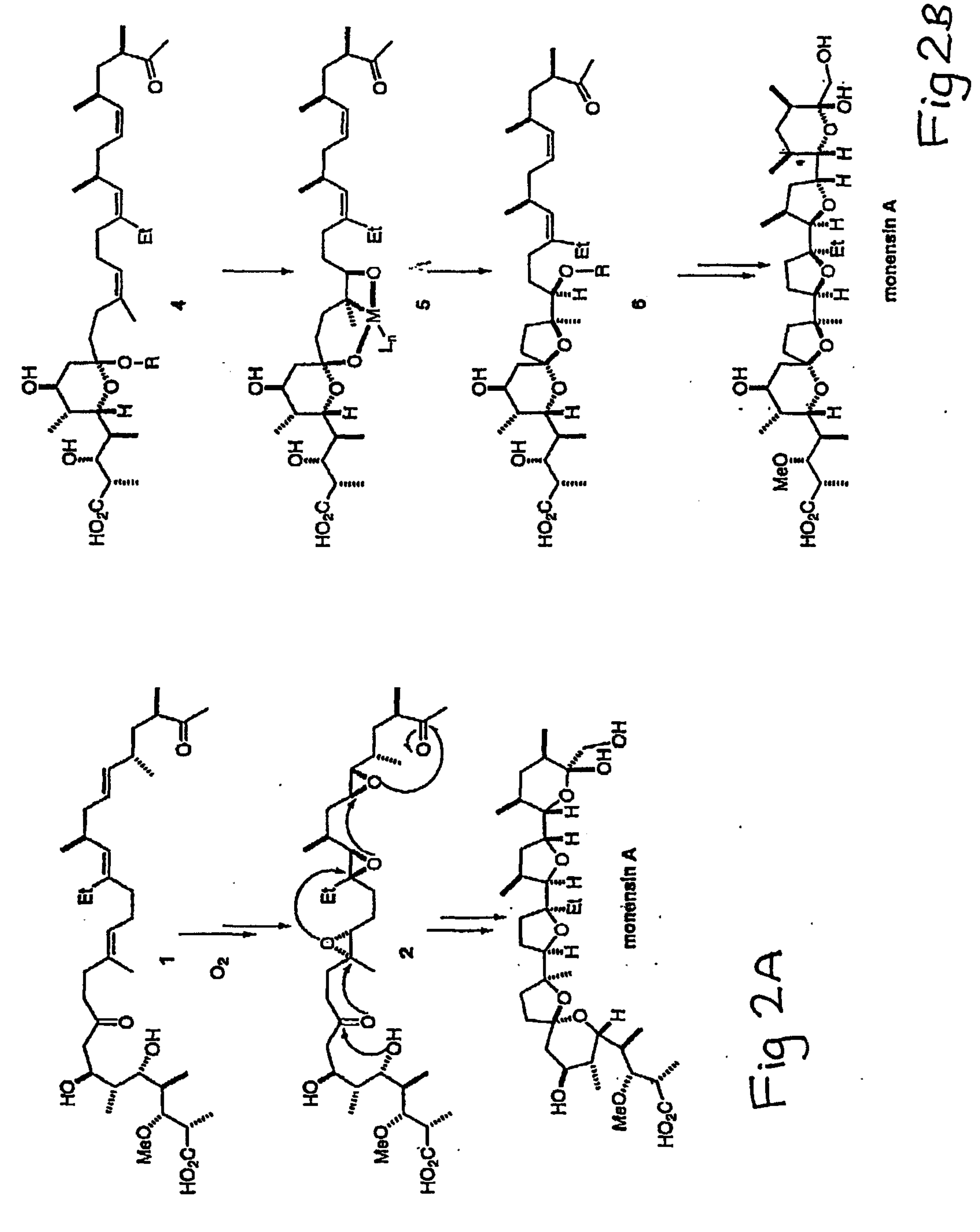


Fig 2A

Fig 2B

Figure 2. Proposed mechanisms for monensin biosynthesis.

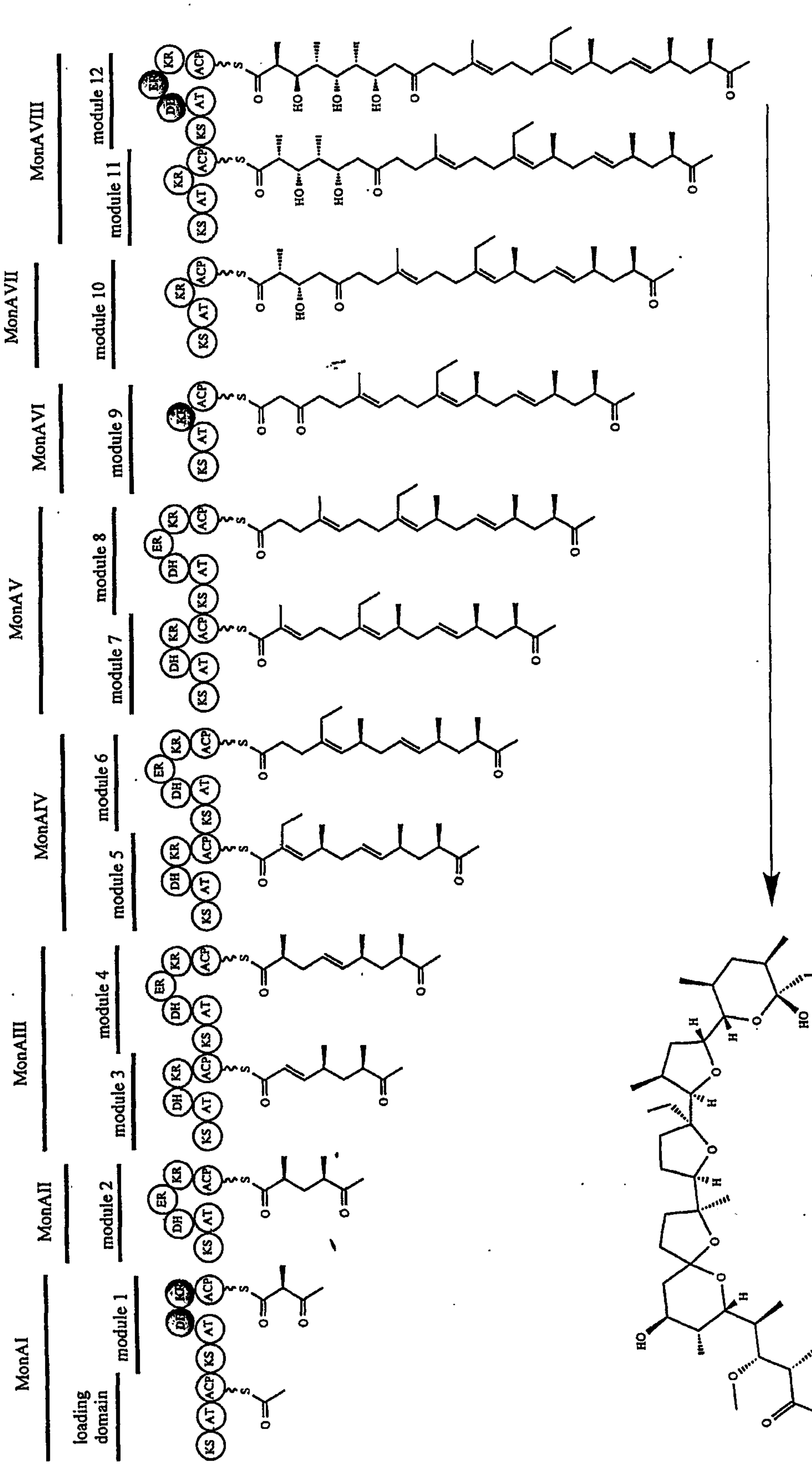


Fig 3

Proposed organisation of the monensin PKS

Organisation of the Monensin Biosynthetic Gene Cluster

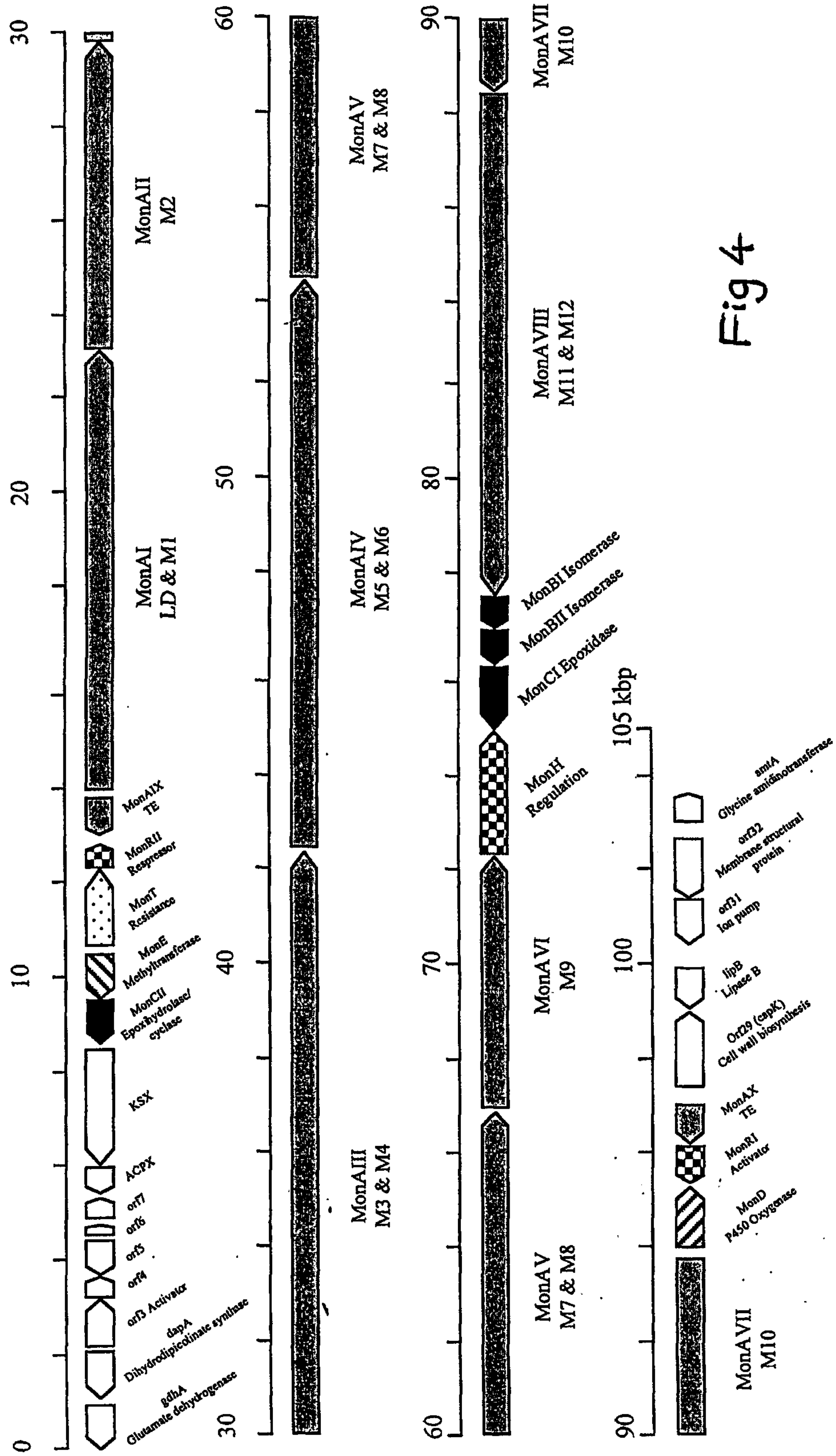


Fig 4

SEQUENCE LISTING

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SUBSTITUTE SHEET (RULE 26)

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SUBSTITUTE SHEET (RULE 26)

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SUBSTITUTE SHEET (RULE 26)

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103501 GGGCCGCGAC CTGTTCGTGA CGCGGAGCAA CGTCGCCAAC CTGCTGGGCA

103551 TCGAGTGGCT GCGCCGCCAC CTTCGGGCCG GAGTACCGCG TGCCACGAGA

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Professor P.F. Leadlay,
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road,
Cambridge.
CB2 1GA

NAME AND ADDRESS OF DEPOSITOR

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
Escherichia coli XL1-Blue MR (MO-CN11)	NCIMB 40956

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 1 July 1998 (date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: NCIMB Ltd.,

Address: 23 St Machar Drive,
Aberdeen,
AB24 3RY,
Scotland.

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):

Date: 9 July 1998

1 Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

Form BP/4 (sole page)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

NAME AND ADDRESS OF DEPOSITOR	
Professor P.F. Leadlay, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge. CB2 1GA	**INTERNATIONAL FORM** **RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT** **issued pursuant to Rule 7.1 by the** **INTERNATIONAL DEPOSITARY AUTHORITY** **identified at the bottom of this page**

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
Escherichia coli XL1-Blue MR (MO-CN33)	NCIMB 40957

II. *SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION*

The microorganism identified under I above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 1 July 1998 (date of the original deposit)[1]

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V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: NCIMB Ltd., Address: 23 St Machar Drive, Aberdeen, AB24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s): Date: 9 July 1998

1 Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

Form BP/4 (sole page)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Professor P.F. Leadlay,
Department of Biochemistry,
University of Cambridge,
80 Tennis Court Road,
Cambridge.
CB2 1GA

NAME AND ADDRESS OF DEPOSITOR

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT issued pursuant to Rule 7.1 by the INTERNATIONAL DEPOSITARY AUTHORITY identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:

Escherichia coli
XL1-Blue MR (MO-CN02)

Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:

NCIMB 40958

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

☐ a scientific description

☒ a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

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Date: 9 July 1998

1 Where Rule 6/4(d) applies, such date is the date on which the status of International Depositary Authority was acquired.

Form BP/4 (sole page)

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Dr. P.F. Leadlay, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge. CB2 1GA	**INTERNATIONAL FORM** **VIABILITY STATEMENT** **issued pursuant to Rule 10.2 by the INTERNATIONAL DEPOSITARY AUTHORITY identified on the following page**

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40956 Date of the deposit or of the transfer[1]: 1 July 1998

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1 July 1998 [2]. On that date, the said microorganism was:

[3]

☒ viable

[3]

☐ no longer viable

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV.	NDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V.	INTERNATIONAL DEPOSITARY AUTHORITY
Name: NCIMB Ltd., Address: 23 St Machar Drive, Aberdeen, A24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s): Date: 9 July 1998

4 Fill in if the information has been requested and if the results of the test were negative.

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Dr. P.F. Leadlay, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge. CB2 1GA

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED

INTERNATIONAL FORM

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the INTERNATIONAL DEPOSITARY AUTHORITY identified on the following page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40957 Date of the deposit or of the transfer[1]: 1 July 1998

III. VIABILITY STATEMENT
The viability of the microorganism identified under II above was tested on 1 July 1998 [2]. On that date, the said microorganism was: [3] ☒ viable [3] ☐ no longer viable

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV. NDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: NCIMB Ltd., Address: 23 St Machar Drive, Aberdeen, A24 3RY, Scotland.	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s): Date: 9 July 1998

4 Fill in if the information has been requested and if the results of the test were negative.

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

Dr. P.F. Leadlay, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge. CB2 1GA	**INTERNATIONAL FORM** **VIABILITY STATEMENT** **issued pursuant to Rule 10.2 by the INTERNATIONAL DEPOSITARY AUTHORITY identified on the following page**

NAME AND ADDRESS OF THE PARTY TO WHOM THE VIABILITY STATEMENT IS ISSUED

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: AS ABOVE Address:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: NCIMB 40958 Date of the deposit or of the transfer[1]: 1 July 1998

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1 July 1998 [2]. On that date, the said microorganism was:

[X] viable [3]

[ ] no longer viable [3]

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2(a)(ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV.	NDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V.	INTERNATIONAL DEPOSITARY AUTHORITY

Name: NCIMB Ltd.,

Address: 23 St Machar Drive,
Aberdeen,
A24 3RY,
Scotland.

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorised official(s):

Date: 9 July 1998

4 Fill in if the information has been requested and if the results of the test were negative.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/52 C12N15/76 C12P17/18 C12P19/44 C12P19/62
C12Q1/68 C07H17/08 C07H19/01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12P C12Q C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, STRAND, EMBL, BIOSIS, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DONOVAN M J ET AL.: "Isolation of DNA involved in monensin biosynthesis by Streptomyces cinnamonensis;" ABSTR. ANNU. MEET. AM. SOC. MICROBIOL. 88 MEET., 1988, page 261 XP000949887	1-3,6-14
Y	abstract	30-38

X	ARROWSMITH T J ET AL.: "Characterisation of actI-homologous DNA encoding polyketide synthase genes from the monensin producer Streptomyces cinnamonensis." MOLECULAR AND GENERAL GENETICS, vol. 234, no. 2, August 1992 (1992-08), pages 254-264, XP002149754	1-3,6-14
Y	page 263, right-hand column, line 1-5	30-38

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2000	08. 01. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van de Kamp, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inten al Application No
PCT/GB 00/02072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MALPARTIDA F ET AL: "Homology between Streptomyces genes coding for synthesis of different polyketides used to clone antibiotic biosynthetic genes" NATURE, vol. 325, no. 6107, 26 February 1987 (1987-02-26), pages 818-821, XP002075972	1-3,6-14
Y	abstract page 819, left-hand column, line 16 -right-hand column, line 1; figure 1	30-38

X	ASHWORTH D M ET AL.: "Selection of a specifically blocked mutant of Streptomyces cinnamonensis: isolation and synthesis of 26-deoxymonensin A." THE JOURNAL OF ANTIBIOTICS, vol. 42, no. 7, July 1989 (1989-07), pages 1088-1099, XP002149776 cited in the application	1-3, 6-14,36
Y	abstract page 1088, line 10-15 scheme 1,2	30-38

X	WO 98 49315 A (KOSAN BIOSCIENCES INC ;UNIV LELAND STANFORD JUNIOR (US)) 5 November 1998 (1998-11-05)	36,45
Y	figure 6G compound #102 example 6 claims 1-10	30-38

X	HOPWOOD D A: "Genetic contributions to understanding polyketide synthases" CHEMICAL REVIEWS, vol. 97, no. 7, November 1997 (1997-11), pages 2465-2497, XP002130647 figures 3,13 table 1 page 2486, paragraph C	36

Y	WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) cited in the application page 5, line 12 -page 10, line 11 claims 1-6	30-38

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZERBE-BURKHARDT K ET AL.: "Cloning, sequencing, expression, and insertional inactivation of the gene for the large subunit of the coenzyme B12-dependent isobutyryl-CoA mutase from Streptomyces cinnamonensis." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 11, 13 March 1998 (1998-03-13), pages 6508-6517, XP002149755 abstract	
A	ROWE C J ET AL: "Construction of new vectors for high-level expression in actinomycetes" GENE, vol. 216, no. 1, August 1998 (1998-08), pages 215-223, XP004149299 cited in the application abstract	
T	WO 00 00500 A (LEADLAY PETER FRANCIS ;CORTES JESUS (GB); STAUNTON JAMES (GB); BIO) 6 January 2000 (2000-01-06) Note: 100.0 % aa seq identity of SEQ ID NO:23 with SEQ ID NO:19 in 920 aa overlap. page 14, line 15-17 page 17, line 15-20 page 24, line 16-20 examples 1,3,26 claim 18	1-3, 6-14, 30-38

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INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see further information sheet invention 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,8-12,14,43,44 (all partially); 2-7,13,15-42, 45 (all completely)

   A DNA sequence comprising the complete monensin (mon) gene cluster, or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with one of the peptides according to SEQ ID NOs 12-33 (AcpX to MonAX as set out in table II), provided that said polypeptide is not all or part of amino acid 1-920 encoded by monAI. Vectors, transformed cells, hybridization probes and their uses.

   Use of mon genes to control expression (monRI), to effect chain release (monAIX and monAX), to provide a desired stereochemical outcome (monBI and monBII), or to provide epoxidase or cyclase activity (monCI and monCII). Mon polypeptides having isomerase activity (MonBI and MonBII), or having chain terminating activity (MonAIX or MonAX), or having epoxidase activity (MonCI), or having cyclase activity (MonCII).

   Processes for producing polyketides involving monensin loading or extension modules or domains. DNA sequences encoding hybrid polyketide synthases containing one or more monensin modules or domains (provided that it is not encoding an ery loading module, the first and second ery extension modules and the ery chain-terminating thioesterase in which the AT domain of the first ery extension module has been substituted by the ethyl malonyl-CoA AT from the monensin synthase), polyketide synthases encoded by said DNA sequences, and polyketide compounds produced by said polyketide synthases. Vectors and transformed cells.

   Methods of producing S. cinnamonensis capable of producing enhanced levels of monensin by overexpressing or amplifying the monRI gene, S. cinnamonensis strains produced thereby, and use of said strains in monensin production.

   Process for expressing a heterologous gene, e.g., a PKS gene, in S. cinnamonensis under the control of monRI.

2. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:5 (GdhA as set out in table II), vectors, transformed cells, hybridization probes and their uses.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

3. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:6 (DapA as set out in table II), vectors, transformed cells, hybridization probes and their uses.

4. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:7 (Orf3 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

5. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:8 (Orf4 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

6. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:9 (Orf5 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

7. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:10 (Orf6 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

8. Claims: 1,8-12,14 (all partially)

   A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:11 (Orf7 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

9. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:34 (Orf29 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

10. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:35 (LipB as set out in table II), vectors, transformed cells, hybridization probes and their uses.

11. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:36 (Orf31 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

12. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:37 (Orf32 as set out in table II), vectors, transformed cells, hybridization probes and their uses.

13. Claims: 1,8-12,14 (all partially)

A DNA sequence or a part or a variant of it which encodes a polypeptide (or part of it) which is at least 80%, preferably at least 90% identical with a peptide according to SEQ ID NO:38 (AmtA as set out in table II), vectors, transformed cells, hybridization probes and their uses.

14. Claims: 43,44 (both partially)

Process for expressing a heterologous gene, e.g., a PKS gene, in S. cinnamonensis under the control of actII/orf4.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte al Application No
PCT/GB 00/02072

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